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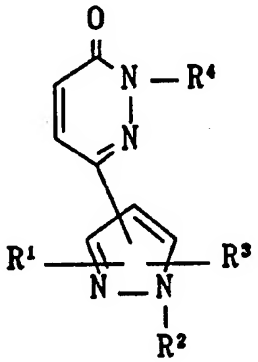
(54) Title: PYRAZOLE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS

(57) Abstract

A pyrazole compound of formula (I), wherein R^1 and R^3 are the same or different and each is independently hydrogen, lower alkyl, ar(lower)alkyl, heterocyclic group, or aryl which may have one or more suitable substituent(s), R^2 is hydrogen, lower alkyl, or ar(lower)alkyl which may have one or more suitable substituent(s), and R^4 is hydrogen or lower alkyl, or a salt thereof. The pyrazole compound (I) and a salt thereof of the present invention are adenosine antagonists and are useful for the prevention and/or the treatment of ischemic heart diseases (e.g. angina, etc.), peripheral vascular diseases (e.g. claudication, etc.), cerebral ischemia, migraine, diabetes, depression, Parkinson's disease, and the like.



(I)

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DESCRIPTION

Pyrazole compounds and pharmaceutical compositions.

Technical Field

The present invention relates to a novel pyrazole compound and a salt thereof. More particularly, it relates to a novel pyrazole compound and a salt thereof, which are adenosine antagonists and are useful for the prevention and/or the treatment of ischemic heart diseases (e.g. angina, etc), peripheral vascular diseases (e.g. claudication, etc), cerebral ischemia, migraine, diabetes, depression, Parkinson's disease, or the like; to a process for the preparation of said pyrazole compound or a salt thereof; to a pharmaceutical composition comprising the same; and to a method for using the same therapeutically in a human being or an animal for the prevention and/or the treatment of the aforesaid diseases.

Disclosure of the Invention

One object of the present invention is to provide a novel pyrazole compound and a salt thereof, which are useful as adenosine antagonists.

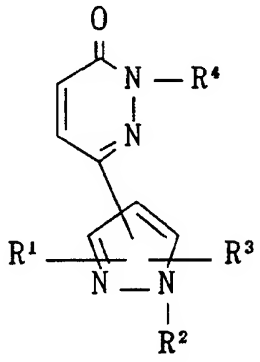
Another object of the present invention is to provide a process for the preparation of said pyrazole compound and a salt thereof.

A further object of the present invention is to provide a pharmaceutical composition containing, as an active ingredient, said pyrazole compound or a salt thereof.

A still further object of the present invention is to provide use of said pyrazole compound or a salt thereof as a medicament such as an adenosine antagonist useful for the prevention and/or the treatment of the aforesaid diseases; to provide a method for using the

same therapeutically in a human being or an animal for the prevention and/or the treatment of the aforesaid diseases.

The novel pyrazole compound of the present invention can be shown by the following formula (I) :



(I)

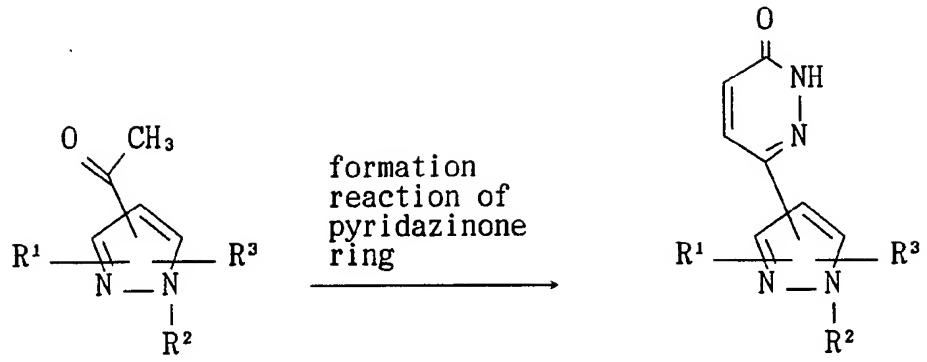
wherein R^1 and R^3 are the same or different and each is independently hydrogen, lower alkyl, ar(lower)alkyl, heterocyclic group, or aryl which may have one or more suitable substituent(s),

R^2 is hydrogen, lower alkyl, or ar(lower)alkyl which may have one or more suitable substituent(s), and

R^4 is hydrogen or lower alkyl.

The object compound (I) or a salt thereof can be prepared according to the following schemes.

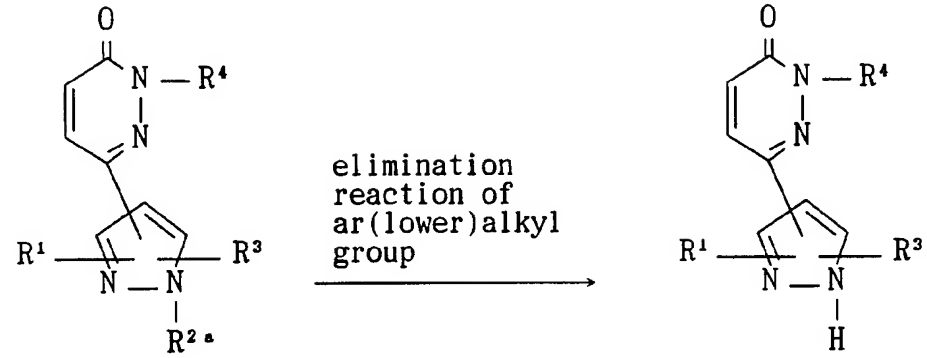
Process 1



(II)
or a salt thereof

(Ia)
or a salt thereof

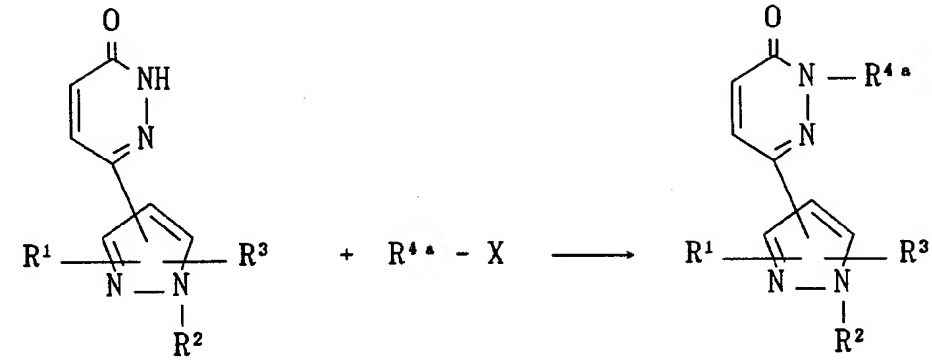
Process 2



(Ib)
or a salt thereof

(Ic)
or a salt thereof

Process 3



(Ia)
or a salt thereof

(Id)
or a salt thereof

wherein R^1, R^2, R^3 and R^4 are each as defined above,

R^{2a} is ar(lower)alkyl,

R^{4a} is lower alkyl, and

X is a leaving group.

The reactions of the aforesaid Processes 1 to 3 can be carried out according to the methods disclosed in Examples in the present specification or the conventional manners in this field of the art.

Some of the compounds of the formula (II) are novel, and they can be prepared according to the methods disclosed in Preparations in the present specification or in a manner similar to them.

It is to be noted that the object compound (I) may include the geometrical isomer(s) due to the double bond(s) and/or the stereo isomer(s) due to the asymmetric carbon atom(s). In this regard, one isomer can be converted to another in a manner conventional in this field of the art.

Suitable salts of the object compound (I) are pharmaceutically acceptable ones and include a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc), an organic acid salt (e.g. acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, etc), a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc), and the like.

Suitable examples and illustrations of the various definitions used in the above and following descriptions of the present specification, which are encompassed within the scope of the present invention, are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atom(s) unless otherwise indicated.

Suitable "lower alkyl" may include straight or branched ones such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl or the like, in which the preferred one may be (C_1-C_5) alkyl and the more preferred one may be methyl, ethyl, isobutyl or pentyl.

Suitable "aryl" may include phenyl, naphthyl, indenyl, anthryl and the like, in which the preferred one may be (C_6-C_{10})aryl and the more preferred one may be phenyl.

This "aryl" may have one or more (preferably 1 to 3) suitable substituent(s) selected from the group consisting of halogen (e.g. fluoro, chloro, bromo, iodo), lower alkyl as mentioned above, lower alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, t-butoxy, pentyloxy, hexyloxy, etc), hydroxy, lower alkyl-silyloxy (e.g. trimethylsilyloxy, t-butyldimethylsilyloxy, etc), phenyl(lower)alkoxy (e.g. phenylmethoxy, phenylethoxy, phenylpropoxy, phenylbutoxy, phenylpentyloxy, phenylhexyloxy, etc), phenyl which may have halo(lower)alkyl (e.g. trifluoromethylphenyl, etc), and the like.

Suitable "ar(lower)alkyl" may include phenyl(lower)alkyl (e.g. benzyl, phenethyl, benzhydryl, trityl, 2-phenylpropyl, 3,4-diphenylbutyl, 2-phenylpentyl, 6-phenylhexyl, etc), and the like.

This "ar(lower)alkyl" may have one or more (preferably 1 to 3)

suitable substituent(s) such as lower alkoxy as mentioned above, and the like.

Suitable "heterocyclic group" may include saturated or unsaturated, monocyclic or polycyclic heterocyclic group such as

unsaturated 3 to 8-membered (more preferably 5 to 7-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, azepinyl (e.g. 1H-azepinyl, etc), pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, dihydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc), etc;

saturated 3 to 8-membered (more preferably 5 to 7-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, perhydroazepinyl (e.g. perhydro-1H-azepinyl, etc), pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, quinoxalinyl, imidazopyridyl [e.g. imidazo[4,5-c]pyridyl, etc], tetrahydroimidazopyridyl [e.g. 4,5,6,7-tetrahydro[4,5-c]pyridyl, etc], etc;

saturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, 7-azabicyclo[2.2.1]heptyl, 3-azabicyclo[3.2.2] nonanyl, etc;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g.

1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc), etc;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc;

unsaturated condensed heterocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc), dihydrothiazinyl, etc;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc;

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 or 2 sulfur atom(s), for example, dihydrooxathiinyl, etc;

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc;

unsaturated condensed heterocyclic group containing an oxygen

atom and 1 or 2 sulfur atom(s), for example benzoxathiinyl, etc; or the like.

In said "heterocyclic group", the preferred one may be unsaturated 3 to 8-membered heteromonocyclic group containing an oxygen atom, and the more preferred one may be furyl.

Suitable "a leaving group" may include halogen as mentioned above, acyloxy such as sulfonyloxy (e.g. mesyloxy, tosyloxy, etc), and the like.

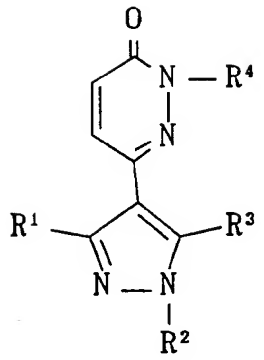
In the pyrazole compound (I) as explained above, the preferred one may be the compound (I) wherein

R^1 and R^3 are the same or different and each is independently hydrogen; lower alkyl; phenyl(lower)alkyl; unsaturated 3 to 8-membered heteromonocyclic group containing an oxygen atom; or phenyl which may have 1 to 3 suitable substituent(s) selected from the group consisting of halogen, lower alkyl, lower alkoxy, hydroxy, lower alkyl-silyloxy, phenyl(lower)alkoxy, and phenyl which may have halo(lower)alkyl;

R^2 is hydrogen, lower alkyl, or phenyl(lower)alkyl which may have lower alkoxy, and

R^4 is hydrogen or lower alkyl.

The more preferred one may be the compound which is shown by the formula (I'):



(I')

wherein R^1, R^2, R^3 and R^4 are each as defined for the above-mentioned preferred compound (I).

The still more preferred one may be the compound (I') wherein

R^1 and R^3 are the same or different and each is independently phenyl which may have 1 to 3 suitable substituent(s) selected from the group consisting of halogen, lower alkyl and lower alkoxy, and

R^2 and R^4 are the same or different and each is independently hydrogen or lower alkyl.

The most preferred one may be the compound (I') wherein

R^1 and R^3 are the same or different and each is independently phenyl which may have 1 to 3 suitable substituent(s) selected from the group consisting of halogen, lower alkyl and lower alkoxy, and

R^2 and R^4 are each hydrogen.

The pharmacological test data of the representative test compound is shown in the following in order to show the utility of the pyrazole compound (I).

[I] Test Method

A radioligand binding assay at the cloned human A_{2a} adenosine receptor was carried out with ^{3}H-CGS 21680 (commercially available).

[II] Test Compound

3,5-Diphenyl-1-methyl-4-(3-oxo-2,3-dihydropyridazin-6-yl)pyrazole

[III] Test Result

The inhibition (%) was more than 80% at the dose of 1.0×10^{-6} (M).

The pyrazole compound (I) and a salt thereof of this invention are useful as adenosine antagonists and for the prevention and/or the treatment of ischemic heart diseases (e.g. angina, etc), peripheral vascular diseases (e.g. claudication, etc), cerebral ischemia, migraine, diabetes, depression, Parkinson's disease, and the like.

The pharmaceutical composition of this invention can be used in the form of a pharmaceutical preparation, for example, in a solid, semisolid or liquid form, which contains the pyrazole compound (I) or a pharmaceutically acceptable salt thereof as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous and intramuscular) administration or insufflation. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, troches, capsules, suppositories, creams, ointments, aerosols, powders for insufflation, solutions, emulsions, suspensions, and any other form suitable for use. Where necessary, any number of auxiliary agents, stabilizing agents, thickening agents, coloring agents and perfumes may be additionally used. The pyrazole compound (I) or a pharmaceutically acceptable salt thereof is included in the pharmaceutical composition in an amount sufficient to produce the desired aforesaid pharmaceutical effect upon the process or condition of diseases.

The composition is preferably applied to a human being or an animal by intravenous, intramuscular, pulmonary, or oral administration, or insufflation. While the therapeutically effective amount of the pyrazole compound (I) varies depending on the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01 - 100 mg of the pyrazole compound (I) per kg weight of a human being or an animal, in the case of intramuscular administration, a daily dose of 0.1 - 100 mg of the pyrazole compound (I) per kg weight of a human being or an animal, in case of oral administration, a daily dose of 0.5 - 100 mg of the pyrazole compound (I) per kg weight of a human being or an animal is generally given for the prevention and/or treatment of the aforesaid diseases.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

A mixture of 3,5-diphenyl-1-methylpyrazole (9.15 g), sulfuric acid (0.1 ml) and acetic anhydride (24 ml) was heated with stirring at 160℃ for 10 hours. The mixture was poured into water. The mixture was made basic with aqueous sodium hydroxide and extracted with dichloromethane. The separated dichloromethane layer was evaporated in vacuo. The residue was chromatographed on silica gel (200 mg) using dichloromethane. The desired fractions were collected and evaporated in vacuo. The residue was recrystallized from a mixture of ethyl acetate and n-hexane to give 4-acetyl-3,5-diphenyl-1-methylpyrazole (8.76 g).

mp : 126-127℃

IR (Nujol) : 1660, 1595 cm^{-1}

NMR (DMSO-d_6, δ) : 1.88 (3H, s), 3.67 (3H, s),
7.39-7.60 (10H, m)

Analysis Calcd. for $C_{18}H_{16}N_2O$:
C 78.24, H 5.84, N 10.41
Found : C 78.70, H 6.03, N 10.06

(+)-APCI/MS : 277 ($M^+ + 1$)

Preparation 2

To a suspension of aluminum chloride (0.27 g) in dry dichloromethane (5 ml) was added dropwise acetyl chloride (0.14 ml) at 5-10℃. 5-(Furan-2-yl)-3-phenylpyrazole (0.21 g) was added to the mixture at the same temperature and then the mixture was stirred for 2 hours. The mixture was evaporated in vacuo. The residue was partitioned between ethyl acetate and water. The separated organic layer was washed with water and saturated aqueous sodium bicarbonate, and evaporated in vacuo. The residue was chromatographed on silica gel (20 ml) using a mixture of ethyl acetate and n-hexane (1:2). The desired fractions were collected and evaporated in vacuo. The residue was recrystallized from a mixture of ethyl acetate and n-hexane to give 4-acetyl-5-(furan-2-yl)-3-phenylpyrazole (0.11 g).

mp : 191-192℃

IR (Nujol) : 3180, 1650, 1530 cm^{-1}

NMR (DMSO-d_6, δ) : 2.46 (3H, s), 7.00 (1H, dd, J=3.6, 14.2Hz),
7.19 (1H, d, J=9.3Hz), 7.38-7.58 (4H, m), 7.82-8.00 (2H, m),
13.70 (1H, s)

Analysis Calcd. for $C_{15}H_{12}N_2O_2 \cdot 1/10H_2O$:

C 70.99, H 4.84, N 11.04

Found : C 70.88, H 4.69, N 11.05

(+)-APCI/MS : 253 ($M^+ + 1$)

The following compounds (Preparations 3 and 4) were obtained in a manner similar to that of Preparation 1.

Preparation 3

4-Acetyl-1-benzyl-3,5-diphenylpyrazole

mp : 91-93℃ (AcOEt : n-hexane)

IR (Nujol) : 1660, 1595 cm^{-1}

NMR (DMSO-d_6, δ) : 1.88 (3H, s), 5.19 (2H, s),
6.98-7.03 (2H, m), 7.25-7.34 (3H, m), 7.39-7.61 (10H, m)

Analysis Calcd. for $C_{24}H_{20}N_2O \cdot 1/4H_2O$:

C 80.76, H 5.78, N 7.85

Found : C 80.84, H 5.87, N 7.92

(+)-APCI/MS : 353 ($M^+ + 1$)

Preparation 4

4-Acetyl-3,5-diphenyl-1-(phenethyl)pyrazole

mp : 100-101℃ (AcOEt : n-hexane)

IR (Nujol) : 1660 cm^{-1}

NMR ($CDCl_3$, δ) : 1.88 (3H, s), 3.13 (2H, t, J=7.3Hz),
4.14 (2H, t, J=7.3Hz), 6.88-7.00 (4H, m), 7.18-7.25 (3H, m),
7.34-7.48 (6H, m), 7.65-7.70 (2H, m)

Analysis Calcd. for $C_{25}H_{22}N_2O \cdot 1/4H_2O$:

C 80.95, H 6.11, N 7.55

Found : C 81.06, H 5.89, N 7.60

(+)-APCI/MS : 367 ($M^+ + 1$)

Preparation 5

A solution of 1M-lithium bis(trimethylsilyl)amide in tetrahydrofuran (213 ml) was added dropwise to a solution of 3'-methoxyacetophenone (27.8 ml) in dry tetrahydrofuran (100 ml) at below 15 ℃ under nitrogen atmosphere. After stirring for 0.5 hour at room temperature, ethyl benzoate was added to the mixture. The mixture was refluxed for 8 hours and evaporated in vacuo. The residue was suspended in n-hexane and then the resulting solid was collected by filtration to give lithium enolate of 1-(3-methoxyphenyl)-3-phenyl-1,3-propanedione (34.6 g). A mixture of the lithium salt thus obtained (34.6 g), hydrazine monohydrate (22.8 g) and ethanol (17 ml) was refluxed for 2 hours and partitioned between ethyl acetate and water. The separated organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was recrystallized from a mixture of ethyl acetate and n-hexane to give 3-(3-methoxyphenyl)-5-phenylpyrazole (18.2 g).

mp : 148-150℃

IR (Nujol) : 3160, 3120, 1620, 1580 cm^{-1}

NMR (DMSO-d_6, δ) : 3.83 (3H, s), 6,80-7.0 (1H, m),
7.21 (1H, s), 7.25-7.40 (6H, m), 7.75-8.0 (2H, m),
13.35 (1H, s)

Analysis Calcd. for $C_{16}H_{14}N_2O \cdot 1/10H_2O$:
C 76.23, H 5.68, N 11.11
Found : C 76.26, H 5.55, N 10.91

(+)-APCI/MS : 251 ($M^+ + 1$)

Preparation 6

Bromine (3.7 ml) was added dropwise to a mixture of 3-(3-methoxyphenyl)-5-phenylpyrazole (17.87 g), sodium acetate (6.45 g) and

acetic acid (180 ml) with stirring at room temperature. After stirring for 15 hours, the mixture was poured into water. The resulting solid was collected by filtration and dissolved in ethyl acetate. The ethyl acetate solution was washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and evaporated in vacuo to give 4-bromo-3-(3-methoxyphenyl)-5-phenylpyrazole (24 g) as an oil.

IR (Film) : 1560 cm^{-1}

NMR ($CDCl_3$, δ) : 3.71 (3H, s), 6.84-6.91 (1H, m), 7.20-7.37 (6H, m), 7.37-7.74 (2H, m)

(+)-APCI/MS : 329 $(M + H)^+$, 331 $(M + H)^+$

The following compounds (Preparations 7 and 8) were obtained in a manner similar to that of Preparation 6.

Preparation 7

4-Bromo-3-(3-methylphenyl)-5-phenylpyrazole

mp : 149-150°C (AcOEt : n-hexane)

IR (Nujol) : 3200, 1600, 1580, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 2.39 (3H, s), 7.20-7.87 (9H, m), 13.70 (1H, s)

Analysis Calcd. for $C_{16}H_{13}BrN_2 \cdot 1/2H_2O$:

C 61.01, H 4.22, N 8.89

Found : C 60.68, H 3.98, N 8.93

(+)-APCI/MS : 313 $(M + H)^+$, 315 $(M + H)^+$

Preparation 8

4-Bromo-3-(3-chlorophenyl)-5-phenylpyrazole

mp : 153-154°C (AcOEt : n-hexane)

IR (Nujol) : 3200, 1600, 1570 cm^{-1}

NMR ($CDCl_3$, δ) : 5.25-7.45 (5H, m), 7.61-7.70 (4H, m)

Analysis Calcd. for $C_{15}H_{10}BrClN_2$:

C 54.00, H 3.02, N 8.40

Found : C 53.64, H 2.84, N 8.34

(+)-APCI/MS : 333 $(M + H)^+$, 335 $(M + H)^+$, 336 $(M + H)^+$

Preparation 9

To a solution of 4-bromo-3-(3-methoxyphenyl)-5-phenylpyrazole (24 g) in dry N,N-dimethylformamide (240 ml) was added 60% sodium hydride (3.06 g) under ice-cooling and nitrogen atmosphere. After stirring for 0.5 hour under the same conditions, trityl chloride (20.3 g) was added to the mixture. The reaction mixture was stirred for 15 hours at room temperature and poured into water. The resulting solid was collected by filtration and dissolved in ethyl acetate. The ethyl acetate solution was washed with brine, dried over anhydrous sodium sulfate, and evaporated in vacuo. The residue was recrystallized from a mixture of ethyl acetate and n-hexane to give a mixture of 4-bromo-3-(3-methoxyphenyl)-5-phenyl-1-tritylpyrazole and 4-bromo-5-(3-methoxyphenyl)-3-phenyl-1-tritylpyrazole (30.2 g).

mp : 91-95℃

IR (Nujol) : 1670, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 3.34, 3.44 (3H, each s), 6.07-6.11 (1H, m), 6.50-6.54 (1H, m), 6.64-7.49 (21H, m), 7.85-7.88 (1H, m)

Analysis Calcd. for $C_{35}H_{27}BrN_2O \cdot 1/2H_2O$:

C 72.42, H 4.86, N 4.83

Found : C 72.09, H 4.92, N 4.83

FAB/MS : 571 $(M + H)^+$, 572 $(M + H)^+$

The following compounds (Preparations 10 and 11) were obtained in

a manner similar to that of Preparation 9.

Preparation 10

A mixture of 4-bromo-3-(3-methylphenyl)-5-phenyl-1-tritylpyrazole and 4-bromo-5-(3-methylphenyl)-3-phenyl-1-tritylpyrazole

mp : 138-141℃ (AcOEt : n-hexane)

IR (Nujol) : 1660, 1590 cm^{-1}

NMR ($CDCl_3$, δ) : 2.00, 2.04, 2.38, 2.43 (3H, each s), 6.14-6.97 (3H, m), 7.00-7.60 (19H, m), 7.78-7.82 (1H, m), 7.98-8.03 (1H, m)

Analysis Calcd. for $C_{35}H_{27}BrN_2 \cdot 1/2H_2O$:

C 74.47, H 5.00, N 4.96

Found : C 74.34, H 4.92, N 5.14

(+)-FAB/MS : 555 $(M + H)^+$, 557 $(M + H)^+$

Preparation 11

A mixture of 4-bromo-3-(3-chlorophenyl)-5-phenyl-1-tritylpyrazole and 4-bromo-5-(3-chlorophenyl)-3-phenyl-1-tritylpyrazole

mp : 148-150℃ (AcOEt : n-hexane)

IR (Nujol) : 1595, 1580 cm^{-1}

NMR ($CDCl_3$, δ) : 6.30-7.50 (22H, m), 7.85-8.10 (2H, m)

Analysis Calcd. for $C_{34}H_{24}BrClN_2$:

C 70.91, H 4.20, N 4.86

Found : C 70.59, H 4.40, N 4.58

(+)-FAB/MS : 575 $(M + H)^+$, 577 $(M + H)^+$

Preparation 12

A solution of 1.7M-butyl lithium in hexane (37 ml) was added dropwise to a solution of 4-bromo-3-(3-methoxyphenyl)-5-phenyl-1-tritylpyrazole and 4-bromo-5-(3-methoxyphenyl)-3-phenyl-1-

tritylpyrazole (30 g) in dry tetrahydrofuran (300 ml) at below -60℃ under nitrogen atmosphere. After stirring for 0.3 hour under the same conditions, the mixture was added dropwise to a solution of acetic anhydride (50 ml) in dry tetrahydrofuran (100 ml) at below -60℃ under nitrogen atmosphere. The mixture was warmed up to room temperature and stirred for 1 hour. 12N-Hydrochloric acid (25 ml) was added to the mixture, and the resulting mixture was refluxed for 2 hours. The reaction mixture was made basic with 28%-ammonium hydroxide and extracted with ethyl acetate. The separated organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (500 ml) using a mixture of ethyl acetate and n-hexane (1:4) as an eluent to give an oil (10.26 g), which was recrystallized from a mixture of ethyl acetate and n-hexane to give 4-acetyl-3-(3-methoxyphenyl)-5-phenylpyrazole (7.8 g).

mp : 130-132℃

IR (Nujol) : 3300, 1675, 1610, 1580 cm^{-1}

NMR (DMSO-d_6, δ) : 2.06 (3H, s), 3.81 (3H, s), 6.95-7.20 (3H, m), 7.30-7.60 (6H, m), 13.61 (1H, s)

(+)-APCI/MS : 293 $(M + H)^+$

The following compounds (Preparations 13 and 14) were obtained in a manner similar to that of Preparation 12.

Preparation 13

4-Acetyl-3-(3-methylphenyl)-5-phenylpyrazole

IR (Nujol) : 1620, 1590, 1570, 1540 cm^{-1}

NMR ($CDCl_3$, δ) : 2.10 (3H, s), 2.36 (3H, s), 7.22-7.44 (7H, m), 7.50-7.58 (2H, m)

(+)-APCI/MS : 277 $(M + H)^+$

Preparation 14

4-Acetyl-3-(3-chlorophenyl)-5-phenylpyrazole

mp : 125-127℃ (AcOEt : n-hexane)

IR (Nujol) : 3170, 1630, 1595, 1560 cm^{-1}

NMR ($CDCl_3$, δ) : 2.09 (3H, s), 7.25-7.53 (9H, m)

Analysis Calcd. for $C_{17}H_{13}ClN_2O$:

C 68.81, H 4.42, N 9.44

Found : C 68.30, H 4.33, N 9.39

(+)-APCI/MS : 297 $(M + H)^+$, 299 $(M + H)^+$

Preparation 15

3-(3-Fluorophenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 5.

mp : 180-182℃ (AcOEt : n-hexane)

IR (Nujol) : 3100, 1610, 1590, 1570 cm^{-1}

NMR (DMSO-d_6, δ) : 6.90-8.00(10H, m), 13.45(1H, s)

Analysis Calcd. for $C_{15}H_{11}FN_2 \cdot 1/4H_2O$:

C 74.22, H 4.78, N 11.55

Found : C 74.56, H 4.48, N 11.69

(+)-APCI/MS : 239 $(M + H)^+$

Preparation 16

3-(2-Chlorophenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 5.

mp : 127-128℃ (AcOEt : n-hexane)

IR (Nujol) : 3210, 1605, 1570 cm^{-1}

NMR ($CDCl_3$, δ) : 6.98(1H, s), 7.28-7.51(6H, m),
7.66-7.71(1H, m), 7.78(2H, d, J=6.7Hz)

Analysis Calcd. for $C_{15}H_{11}ClN_2$:

C 70.73, H 4.35, N 11.00

Found : C 70.30, H 4.14, N 11.11

(+)-APCI/MS : 255 $(M + H)^+$

Preparation 17

3-(3,4-Dichlorophenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 5.

mp : 215-216℃ (AcOEt : n-hexane)

IR (Nujol) : 3230, 1590, 1570 cm^{-1}

NMR (DMSO-d_6, δ) : 7.34-8.11(9H, m), 13.53(1H, s)

Analysis Calcd. for $C_{15}H_{10}Cl_2N_2$:

C 62.31, H 3.49, N 9.69

Found : C 62.10, H 3.32, N 9.59

(+)-APCI/MS : 289 $(M + H)^+$

Preparation 18

3-(3,5-Dichlorophenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 5.

mp : 219-220℃ (AcOEt : n-hexane)

IR (Nujol) : 3220, 1590, 1570, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 7.35-7.54(5H, m), 7.78-7.91(4H, m), 13.40-13.70(1H,m)

Analysis Calcd. for $C_{15}H_{10}Cl_2N_2 \cdot 1/4H_2O$:

C 61.35, H 3.60, N 9.54

Found : C 61.51, H 3.19, N 9.75

(+)-APCI/MS : 289 $(M + H)^+$

Preparation 19

3-(3-Ethylphenyl)-5-phenylpyrazole was obtained in a manner

similar to that of Preparation 5.

mp : 104-105℃ (AcOEt : n-hexane)

IR (Nujol) : 1605, 1585, 1570 cm^{-1}

NMR (DMSO-d_6, δ) : 1.24(3H, t, J=7.6Hz), 2.67(2H, q, J=7.6Hz), 7.18(1H, s), 7.19-7.20(1H, m), 7.32-7.46(4H, m), 7.63-7.71(2H, m), 7.83-7.85(2H, m), 13.31(1H, s)

Analysis Calcd. for $C_{17}H_{16}N_2 \cdot 1/4H_2O$:

C 80.76, H 6.58, N 11.08

Found : C 80.69, H 6.25 N 11.26

(+)-APCI/MS : 249 $(M + H)^+$

Preparation 20

3-(3-Ethoxyphenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 5.

oil

IR (Film) : 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.36(3H, t, J=6.9Hz), 3.96(2H, q, J=6.9Hz), 6.78(1H, s), 6.81-6.89(1H, m), 7.25-7.54(6H, m), 7.66-7.71(2H, m)

(+)-APCI/MS : 265 $(M + H)^+$

Preparation 21

3-(3-Isopropoxyphenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 5.

oil

IR (Film) : 1590 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30(6H, d, J=6.1Hz), 4.43(1H, sep, J=6.1Hz), 6.78(1H, s), 6.81-6.87(1H, m), 7.24-7.42(6H, m), 7.67-7.72(2H, m)

(+)-APCI/MS : 279 $(M + H)^+$

Preparation 22

3,5-Bis(3-chlorophenyl)pyrazole was obtained in a manner similar to that of Preparation 5.

mp : 221-222℃ (AcOEt : n-hexane)

IR (Nujol) : 1600, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 7.30-7.60(5H, m), 7.81(2H, d, J=7.5Hz), 7.92(2H, s), 13.60(1H, s)

Analysis Calcd. for $C_{15}H_{10}Cl_2N_2 \cdot 1/4H_2O$:

C 61.35, H 3.60, N 9.54

Found : C 61.45, H 3.32, N 9.54

(+)-APCI/MS : 289 $(M + H)^+$

Preparation 23

4-Bromo-3-(3-fluorophenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 6.

mp : 170-172℃ (AcOEt : n-hexane)

IR (Nujol) : 3170, 1610, 1580 cm^{-1}

NMR (DMSO-d_6, δ) : 7.20-7.90(9H, m), 13.87(1H, s)

Analysis Calcd. for $C_{15}H_{10}BrFN_2$:

C 56.81, H 3.18, N 8.83

Found : C 56.54, H 3.14, N 8.80

(+)-APCI/MS : 319 $(M + H)^+$

Preparation 24

4-Bromo-3-(2-chlorophenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 6.

mp : 77-79℃ (AcOEt : n-hexane)

IR (Nujol) : 1600, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 7.40-7.66(8H, m), 7.80(1H, d, J=6.7Hz),
7.90(1H, d, J=6.7Hz), 13.68, 13.79(total 1H, each s)

Analysis Calcd. for $C_{15}H_{10}BrClN_2 \cdot 0.6H_2O$:
C 52.31, H 3.28, N 8.13
Found : C 52.64, H 2.95, N 8.04

(+)-APCI/MS : 335 $(M + H)^+$

Preparation 25

4-Bromo-3-(3,4-dichlorophenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 6.

mp : 180-182℃ (AcOEt : n-hexane)

IR (Nujol) : 3330, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 7.40-8.0(7H, m), 8.07(1H, s), 13.93(1H, s)

Analysis Calcd. for $C_{15}H_9BrCl_2N_2 \cdot 1/10AcOEt \cdot 1/5CHCl_3$:
C 46.76, H 2.51, N 6.99
Found : C 47.32, H 2.23, N 6.52

(+)-APCI/MS : 369 $(M + H)^+$

Preparation 26

4-Bromo-3-(3,5-dichlorophenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 6.

mp : 205-206℃ (AcOEt : n-hexane)

IR (Nujol) : 3320, 1590, 1555 cm^{-1}

NMR (DMSO-d_6, δ) : 7.43-7.59(3H, m), 7.69-7.76(2H, m),
7.80(1H, d, J=1.9Hz), 7.80(2H, d, J=1.9Hz)

Analysis Calcd. for $C_{15}H_9BrCl_2N_2 \cdot 1/4H_2O$:
C 48.36, H 2.57, N 7.52
Found : C 48.21, H 2.18, N 7.49

(+)-APCI/MS : 369 $(M + H)^+$

Preparation 27

4-Bromo-3-(2-methylphenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 6.

oil

IR (Film) : 1595, 1550 cm^{-1}

NMR ($CDCl_3$, δ) : 2.27(3H, s), 7.23-7.47(7H, m), 7.79-7.85(2H, m)

(+)-APCI/MS : 313 $(M + H)^+$

Preparation 28

4-Bromo-3-(3-ethylphenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 6.

oil

IR (Film) : 1600, 1580, 1560 cm^{-1}

NMR ($CDCl_3$, δ) : 1.21(3H, t, J=7.6Hz), 2.64(2H, q, J=7.6Hz), 7.22-7.41(5H, m), 7.51-7.55(2H, m), 7.69-7.74(2H, m)

(+)-APCI/MS : 327 (M + H)

Preparation 29

4-Bromo-3-(3-ethoxyphenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 6.

mp : 89-90℃ (AcOEt : n-hexane)

IR (Nujol) : 3150, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 1.36(3H, t, J=7.0Hz), 4.07-4.13(2H, m), 6.95-7.10(1H, m), 7.32-7.56(6H, m), 7.76(1H, d, J=7.5Hz), 7.84(1H, d, J=6.9Hz), 13.73(1H, s)

Analysis Calcd. for $C_{17}H_{15}BrN_2O \cdot AcOEt$:

C 59.36, H 4.52, N 7.95

Found : C 59.41, H 4.71, N 7.48

(+)-APCI/MS : 343 $(M + H)^+$

Preparation 30

4-Bromo-3-(3-isopropoxyphenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 6.

oil

IR (Film) : 1600, 1580 cm^{-1}

NMR (DMSO-d_6, δ) : 1.31(6H, d, J=6.0Hz), 4.60-4.80(1H, m), 6.99-7.04(1H, m), 7.30-7.99(8H, m), 13.72(1H, s)

(+)-APCI/MS : 357 $(M + H)^+$

Preparation 31

3,5-Bis(3-chlorophenyl)-4-bromopyrazole was obtained in a manner similar to that of Preparation 6.

mp : 192-193℃ ($CHCl_3$: n-hexane)

IR (Nujol) : 3340, 3225, 1600, 1570 cm^{-1}

NMR (DMSO-d_6, δ) : 7.50-7.65(4H, m), 7.70-7.90(4H, m), 13.99(1H, s)

Analysis Calcd. for $C_{15}H_9BrCl_2N_2$:

C 48.95, H 2.46, N 7.61

Found : C 49.13, H 2.20, N 7.58

(+)-APCI/MS : 369 $(M + H)^+$

Preparation 32

A mixture of 4-bromo-3-(3-fluorophenyl)-5-phenyl-1-triphenylmethylpyrazole and 4-bromo-5-(3-fluorophenyl)-3-phenyl-1-triphenylmethylpyrazole was obtained in a manner similar to that of Preparation 9.

mp : 147-150℃ (AcOEt : n-hexane)

IR (Nujol) : 1610, 1580 cm^{-1}

NMR (DMSO-d_6, δ) : 6.19-7.87(24H, m)

Analysis Calcd. for $C_{34}H_{24}BrFN_2 \cdot 0.7H_2O$:

C 71.38, H 4.47, N 4.90

Found : C 70.99, H 3.98, N 4.86

(+)-APCI/MS : 559 $(M + H)^+$

Preparation 33

A mixture of 4-bromo-3-(2-chlorophenyl)-5-phenyl-1-triphenylmethylpyrazole and 4-bromo-5-(2-chlorophenyl)-3-phenyl-1-triphenylmethylpyrazole was obtained in a manner similar to that of Preparation 9.

mp : 210-214℃ (AcOEt : n-hexane)

IR (Nujol) : 1595 cm^{-1}

NMR ($CDCl_3$, δ) : 6.57-7.99(24H, m)

Analysis Calcd. for $C_{34}H_{24}BrClN_2$:

C 70.91, H 4.20, N 4.86

Found : C 70.58, H 4.29, N 4.79

(+)-APCI/MS : 578 $(M + H)^+$

Preparation 34

A mixture of 4-bromo-3-(4-chlorophenyl)-5-phenyl-1-triphenylmethylpyrazole and 4-bromo-5-(4-chlorophenyl)-3-phenyl-1-triphenylmethylpyrazole was obtained in a manner similar to that of Preparation 9.

mp : 186-191℃ (AcOEt : n-hexane)

IR (Nujol) : 1595 cm^{-1}

NMR (DMSO-d_6, δ) : 6.27-8.02(24H, m)

Preparation 35

A mixture of 4-bromo-3-(3,4-dichlorophenyl)-5-phenyl-1-triphenylmethylpyrazole and 4-bromo-5-(3,4-dichlorophenyl)-3-phenyl-1-

triphenylmethylpyrazole was obtained in a manner similar to that of Preparation 9.

mp : 169-174℃ (AcOEt : n-hexane)

IR (Nujol) : 1595, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 6.49-8.04(24H, m)

Analysis Calcd. for $C_{34}H_{23}BrCl_2N_2 \cdot 1/4H_2O$:

C 66.42, H 3.85, N 4.56

Found : C 66.22, H 3.74, N 4.40

(+)-APCI/MS : 611 $(M + H)^+$

Preparation 36

A mixture of 4-bromo-3-(3,5-dichlorophenyl)-5-phenyl-1-triphenylmethylpyrazole and 4-bromo-5-(3,5-dichlorophenyl)-3-phenyl-1-triphenylmethylpyrazole was obtained in a manner similar to that of Preparation 9.

mp : 175-176℃ (AcOEt : n-hexane)

IR (Nujol) : 1590, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 6.48-7.86(23H, m)

Analysis Calcd. for $C_{34}H_{33}BrCl_2N_2$:

C 65.82, H 5.36, N 4.51

Found : C 66.06, H 3.41, N 4.51

(+)-FAB/MS : 611 $(M + H)^+$

Preparation 37

A mixture of 4-bromo-3-(4-methylphenyl)-5-phenyl-1-triphenylmethylpyrazole and 4-bromo-5-(4-methylphenyl)-3-phenyl-1-triphenylmethylpyrazole was obtained in a manner similar to that of Preparation 9.

mp : 183-185℃ (AcOEt : n-hexane)

IR (Nujol) : 1590 cm^{-1}

NMR ($CDCl_3$, δ) : 2.17, 2.36(3H, s), 7.40-8.03(24H, m)

Analysis Calcd. for $C_{35}H_{27}BrN_2$:

C 75.67, H 4.90, N 5.04

Found : C 75.24, H 4.74, N 4.99

(+)-APCI/MS : 557 $(M + H)^+$

Preparation 38

A mixture of 4-bromo-3-(2-methylphenyl)-5-phenyl-1-triphenylmethylpyrazole and 4-bromo-5-(2-methylphenyl)-3-phenyl-1-triphenylmethylpyrazole was obtained in a manner similar to that of Preparation 9.

mp : 177-179℃ (AcOEt : n-hexane)

IR (Nujol) : 1595, 1525 cm^{-1}

NMR (DMSO-d_6, δ) : 1.82, 2.28(3H, s), 6.53-7.84(24H, m)

Analysis Calcd. for $C_{35}H_{27}BrN_2 \cdot 1/3H_2O$:

C 74.87, H 4.97, N 4.99

Found : C 74.89, H 4.67, N 4.98

FAB/MS : 556 $(M + H)^+$

Preparation 39

A mixture of 4-bromo-3-(3-ethylphenyl)-5-phenyl-1-triphenylmethylpyrazole and 4-bromo-5-(3-ethylphenyl)-3-phenyl-1-triphenylmethylpyrazole was obtained in a manner similar to that of Preparation 9.

mp : 154-157℃ (AcOEt : n-hexane)

IR (Nujol) : 1590 cm^{-1}

NMR ($CDCl_3$, δ) : 1.22-1.29(3H, m), 2.32(2H, q, J=7.8Hz), 6.38-8.03(24H, m)

Analysis Calcd. for $C_{36}H_{29}BrN_2 \cdot 1/2H_2O$:

C 74.74, H 5.26, N 4.84

Found : C 74.91, H 5.16, N 4.78

Preparation 40

A mixture of 4-bromo-3-(4-methoxyphenyl)-5-phenyl-1-triphenylmethylpyrazole and 4-bromo-5-(4-methoxyphenyl)-3-phenyl-1-triphenylmethylpyrazole was obtained in a manner similar to that of Preparation 9.

mp : 223-230℃ (AcOEt : n-hexane)

IR (Nujol) : 1645, 1610, 1570, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 3.63, 3.79(3H, s), 6.37-7.86(24H, m)

Analysis Calcd. for $C_{35}H_{27}BrN_2O \cdot 0.6H_2O$:

C 72.19, H 4.88, N 4.81

Found : C 71.71, H 4.56, N 5.02

(+)-APCI/MS : 571 $(M + H)^+$

Preparation 41

A mixture of 4-bromo-5-(3-ethoxyphenyl)-3-phenyl-1-triphenylmethylpyrazole and 4-bromo-3-(3-ethoxyphenyl)-5-phenyl-1-triphenylmethylpyrazole was obtained in a manner similar to that of Preparation 9.

mp : 108-110℃ (AcOEt : n-hexane)

IR (Nujol) : 1595 cm^{-1}

NMR (DMSO-d_6, δ) : 1.13-1.22(3H, m), 3.66-4.08(2H, m),
6.07-7.88(24H, m)

Analysis Calcd. for $C_{36}H_{29}BrN_2O \cdot 1/2H_2O$:

C 72.73, H 5.09, N 4.71

Found : C 72.57, H 5.31, N 4.55

(+)-FAB/MS : 585 $(M + H)^+$

Preparation 42

A mixture of 4-bromo-3-(3-isopropoxyphenyl)-5-phenyl-1-triphenylmethylpyrazole and 4-bromo-5-(3-isopropoxyphenyl)-3-phenyl-1-triphenylmethylpyrazole was obtained in a manner similar to that of Preparation 9.

mp : 125-127℃ (AcOEt : n-hexane)

IR (Nujol) : 1595, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 1.09, 1.27(each 6H, d, d, J=5.9Hz, J=5.9Hz),
4.15, 4.59(each 1H, sep, sep, J=5.9Hz, J=5.9Hz),
6.04-7.87(24H, m)

Analysis Calcd. for $C_{37}H_{31}BrN_2O \cdot 1/2H_2O$:
C 73.02, H 5.30, N 4.60
Found : C 73.23, H 5.10, N 4.65

(+)-FAB/MS : 599 $(M + H)^+$

Preparation 43

3,5-Bis(3-chlorophenyl)-4-bromo-1-triphenylmethylpyrazole was obtained in a manner similar to that of Preparation 9.

mp : 179-180℃ (AcOEt : n-hexane)

IR (Nujol) : 1595, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 6.30-6.35(1H, m), 6.66(1H, d, J=7.7Hz),
6.97-7.29(17H, m), 7.48-7.52(2H, m), 7.81-7.86(2H, m)

Analysis Calcd. for $C_{34}H_{23}BrCl_2N_2$:
C 66.90, H 3.80, N 4.59
Found : C 67.20, H 3.64, N 4.57

(+)-APCI/MS : 609 $(M + H)^+$

Preparation 44

3,5-Bis(4-methoxyphenyl)-4-bromo-1-triphenylmethylpyrazole was obtained in a manner similar to that of Preparation 9.

mp : 192-195℃ (AcOEt : n-hexane)

IR (Nujol) : 1600, 1570, 1515 cm^{-1}

NMR (DMSO-d_6, δ) : 3.63(3H, s), 3.76(3H, s), 6.35-6.50(4H, m), 7.00-7.10(8H, m), 7.20-7.30(9H, m), 7.74-7.79(2H, m)

Analysis Calcd. for $C_{36}H_{29}BrN_2O_2 \cdot 1/2H_2O$:

C 70.82, H 4.95, N 4.59

Found : C 70.86, H 4.66, N 4.60

FAB/MS : 603 $(M + H)^+$

Preparation 45

4-Acetyl-3-(3-fluorophenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 12.

mp : 153-154℃ (AcOEt : n-hexane)

IR (Nujol) : 3170, 3090, 1630, 1580 cm^{-1}

NMR (DMSO-d_6, δ) : 2.08(3H, s), 7.24-7.32(1H, m), 7.41-7.60(8H, m), 13.70(1H, s)

Analysis Calcd. for $C_{17}H_{13}FN_2O$:

C 72.85, H 4.67, N 9.99

Found : C 72.79, H 4.63, N 9.89

(+)-APCI/MS : 281 $(M + H)^+$

Preparation 46

4-Acetyl-3-(2-chlorophenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 12.

oil

IR (Film) : 1650, 1560 cm^{-1}

NMR ($CDCl_3$, δ) : 2.03(3H, s), 7.26-7.56(9H, m)

(+)-APCI/MS : 297 $(M + H)^+$

Preparation 47

4-Acetyl-3,5-bis(3-chlorophenyl)pyrazole was obtained in a manner similar to that of Preparation 12.

mp : 123-124℃ (AcOEt : n-hexane)

IR (Nujol) : 3175, 3080, 1630, 1600, 1570 cm^{-1}

NMR (DMSO-d_6, δ) : 2.08(3H, s), 7.42-7.59(6H, m),
7.67(2H, s), 13.82(1H, s)

Analysis Calcd. for $C_{17}H_{12}Cl_2N_2O$:
C 61.65, H 3.65, N 8.45
Found : C 61.19, H 3.29, N 8.43

(+)-APCI/MS : 331 $(M + H)^+$

Preparation 48

4-Acetyl-3-(4-chlorophenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 12.

mp : 155-158℃ (AcOEt : n-hexane)

IR (Nujol) : 3170, 1640, 1545 cm^{-1}

NMR ($CDCl_3$, δ) : 2.09(3H, s), 7.32-7.50(9H, m)

Analysis Calcd. for $C_{17}H_{13}ClN_2O$:
C 68.81, H 4.42, N 9.44
Found : C 68.94, H 4.45, N 9.36

(+)-APCI/MS : 297 $(M + H)^+$

Preparation 49

4-Acetyl-3-(3,4-dichlorophenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 12.

mp : 172-173℃ (AcOEt : n-hexane)

IR (Nujol) : 3150, 3080, 1630, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 2.05(3H, s), 7.49-7.61(6H, m),
7.72(1H, d, J=8.4Hz), 7.89(1H, d, J=1.9Hz), 13.77(1H, s)

Analysis Calcd. for $C_{17}H_{12}Cl_2N_2O \cdot 1/4H_2O$:
C 60.82, H 3.75, N 8.34
Found : C 60.88, H 3.44, N 8.33

(+)-APCI/MS : 331 $(M + H)^+$

Preparation 50

4-Acetyl-3-(3,5-dichlorophenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 12.

mp : 171-173℃ (AcOEt : n-hexane)

IR (Nujol) : 1700, 1630, 1585, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 2.06(3H, s), 7.40-7.90(8H, m), 13.81(1H, s)

Analysis Calcd. for $C_{17}H_{12}Cl_2N_2O$:
C 61.65, H 3.65, N 8.46
Found : C 61.22, H 3.45, N 8.30

(+)-APCI/MS : 331 $(M + H)^+$

Preparation 51

4-Acetyl-3-(2-methylphenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 12.

mp : 137-139℃ (AcOEt : n-hexane)

IR (Nujol) : 3170, 3090, 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 1.88(3H, s), 2.18(3H, s), 7.27-7.64(9H, m),
13.47, 13.62(total 1H, each s)

Analysis Calcd. for $C_{18}H_{16}N_2O \cdot 1/5H_2O$:
C 77.23, H 5.76, N 10.01
Found : C 77.40, H 5.67, N 9.99

(+)-APCI/MS : 277 $(M + H)^+$

Preparation 52

4-Acetyl-3-(4-methylphenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 12.

mp : 152-153℃ (AcOEt : n-hexane)

IR (Nujol) : 3200, 1640, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.05(3H, s), 2.36, 2.38(total 3H, each s), 7.22-7.55(9H, m), 13.53(1H, s)

Analysis Calcd. for $C_{18}H_{16}N_2O \cdot 0.1H_2O$:

C 77.73, H 5.87, N 10.07

Found : C 77.71, H 5.73, N 9.66

(+)-APCI/MS : 277 $(M + H)^+$

Preparation 53

4-Acetyl-3-(3-ethylphenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 12.

oil

IR (Film) : 1660, 1605, 1585, 1550 cm^{-1}

NMR ($CDCl_3$, δ) : 1.24(3H, t, J=7.6Hz), 2.03(3H, s), 2.62(2H, q, J=7.6Hz), 7.23-7.44(7H, m), 7.48-7.55(2H, m)

(+)-APCI/MS : 291 $(M + H)^+$

Preparation 54

4-Acetyl-3-(4-methoxyphenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 12.

mp : 147-149℃ (AcOEt : n-hexane)

IR (Nujol) : 3170, 1640, 1610, 1585, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 2.04(3H, s), 3.81(3H, s), 7.04(2H, d, J=8.4Hz), 7.40-7.60(7H, m), 13.51(1H, s)

Analysis Calcd. for $C_{18}H_{16}N_2O_2 \cdot 1/4H_2O$:

C 72.83, H 5.60, N 9.44

Found : C 72.78, H 5.29, N 9.40

(+)-APCI/MS : 293 $(M + H)^+$

Preparation 55

4-Acetyl-3-(3-ethoxyphenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 12.

oil

IR (Film) : 1660, 1600, 1575 cm^{-1}

NMR (DMSO-d_6, δ) : 1.35(3H, t, J=7.0Hz), 2.06(3H, s), 4.07(2H, q, J=7.0Hz), 6.99-7.13(3H, m), 7.33-7.59(6H, m)

(+)-APCI/MS : 307 $(M + H)^+$

Preparation 56

4-Acetyl-3-(3-isopropoxyphenyl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 12.

oil

IR (Film) : 1660, 1595, 1575 cm^{-1}

NMR (DMSO-d_6, δ) : 1.30(6H, d, J=6.0Hz), 2.07(3H, s), 4.66(1H, sep, J=6.0Hz), 6.98-7.11(3H, m), 7.32-7.60(6H, m)

(+)-APCI/MS : 321 $(M + H)^+$

Preparation 57

4-Acetyl-3,5-bis(4-methoxyphenyl)pyrazole was obtained in a manner similar to that of Preparation 12.

mp : 182-184℃ (AcOEt)

IR (Nujol) : 3200, 1640, 1610, 1575, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 2.03(3H, s), 3.81(6H, s), 7.03(4H, d, J=8.6Hz), 7.51(4H, d, J=8.6Hz), 13.39(1H, s)

Analysis Calcd. for $C_{19}H_{18}N_2O_3$:

C 70.79, H 5.63, N 8.69

Found : C 71.05, H 5.48, N 8.68

(+)-APCI/MS : 323 $(M + H)^+$

Preparation 58

4-Acetyl-3,5-diphenyl-1-ethylpyrazole was obtained in a manner similar to that of Preparation 1.

mp : 134-135℃ (AcOEt : n-hexane)

IR (Nujol) : 1665 cm^{-1}

NMR ($CDCl_3$, δ) : 1.37(3H, t, J=7.3Hz), 1.94(3H, s), 4.00(2H, q, J=7.3Hz), 7.25-7.55(8H, m), 7.61-7.66(2H, m)

Analysis Calcd. for $C_{19}H_{18}N_2O$:

C 78.59, H 6.25, N 9.65

Found : C 78.21, H 6.28, N 9.60

(+)-APCI/MS : 291 $(M + H)^+$

Preparation 59

4-Acetyl-3,5-diphenyl-1-isobutylpyrazole was obtained in a manner similar to that of Preparation 1.

mp : 64-65℃ (AcOEt : n-hexane)

IR (Nujol) : 1650 cm^{-1}

NMR ($CDCl_3$, δ) : 0.80(6H, d, J=6.7Hz), 1.93(3H, s), 2.15-2.40(1H, m), 3.76(2H, d, J=7.5Hz), 7.39-7.53(8H, m), 7.61-7.66(2H, m)

Analysis Calcd. for $C_{21}H_{22}N_2O$:

C 79.21, H 6.96, N 8.80

Found : C 79.41, H 7.12, N 8.82

(+)-APCI/MS : 319 $(M + H)^+$

Preparation 60

4-Acetyl-3,5-diphenyl-1-n-pentylpyrazole was obtained in a manner similar to that of Preparation 1.

oil

IR (Film) : 1665, 1605, 1575, 1525 cm^{-1}

NMR ($CDCl_3$, δ) : 0.82(3H, t, J=6.5Hz), 1.16-1.29(4H, m), 1.71-1.86(2H, m), 1.94(3H, s), 3.93(2H, t, J=7.4Hz), 7.37-7.54(8H, m), 7.61-7.66(2H, m)

(+)-APCI/MS : 333 $(M + H)^+$

Preparation 61

To a mixture of 4-bromo-3,5-diphenylpyrazole (28.49 g) and dry N,N-dimethylformamide (380 ml) was added 60% sodium hydride (4.38 g) with stirring at below 10℃ under nitrogen atmosphere. After stirring for 0.5 hour under the same conditions, triphenylmethyl-chloride (29.2 g) was added to the mixture and then the mixture was stirred for 5 hours. The mixture was poured into water. The resulting solid was collected by filtration and recrystallized from a mixture of ethyl acetate and n-hexane to give 4-bromo-3,5-diphenyl-1-triphenylmethylpyrazole (41.95 g).

mp : 186-187℃

NMR ($CDCl_3$, δ) : 6.54-6.59(2H, m), 6.84-6.91(2H, m), 6.97-7.39(19H, m), 7.99-8.03(2H, m)

Analysis Calcd. for $C_{34}H_{25}BrN_2 \cdot 1/4H_2O$:

C 74.80, H 4.71, N 5.13

Found : C 74.78, H 4.66, N 5.10

(+)-FAB/MS : 541 $(M + H)^+$

Preparation 62

A solution of 1.7M butyl lithium in n-hexane (54 ml) was added dropwise to a solution of 4-bromo-3,5-diphenyl-1-triphenylmethyl-pyrazole (41.9 g) in dry tetrahydrofuran (300 ml) at below -60℃ under nitrogen atmosphere. After stirring for 0.25 hour under the same conditions, the mixture was added dropwise to a solution of acetic anhydride (73 ml) in dry tetrahydrofuran (140 ml) at below -60℃ under nitrogen atmosphere. After stirring for 3 hours under the same conditions and at room temperature for 16 hours, 12N hydrochloric acid (20 ml) was added to the mixture, which was refluxed for 2 hours. The reaction mixture was partitioned between ethyl acetate and water. The separated organic layer was washed with water and 28% ammonium hydroxide, dried over magnesium sulfate, and evaporated in vacuo. The residue was recrystallized from a mixture of ethyl acetate and n-hexane to give 4-acetyl-3,5-diphenylpyrazole (17.8 g).

mp : 143-145℃

IR (Nujol) : 3200, 1635, 1550 cm^{-1}

NMR ($CDCl_3$, δ) : 2.07(3H, s), 7.25-7.48(10H, m)

(+)-APCI/MS : 263 $(M + H)^+$

Preparation 63

60% Sodium hydride (80 mg) was added to a solution of 4-acetyl-3,5-diphenylpyrazole (0.50 g) in dry N,N-dimethylformamide (5 ml) with stirring under ice-cooling. 4-Methoxybenzyl chloride (0.26 ml) was added to the mixture under the same conditions and then the mixture was stirred at room temperature for 62 hours. The mixture was partitioned between ethyl acetate and water. The separated organic layer was evaporated in vacuo to give 4-acetyl-3,5-diphenyl-1-(4-

methoxybenzyl)pyrazole (0.74 g) as an oil.

IR (Nujol) : 1660, 1605, 1580, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 1.94(3H, s), 3.77(3H, s), 5.10(2H, s), 6.75-6.80(2H, m), 6.95-6.99(2H, m), 7.25-7.67(10H, m)

(+)-APCI/MS : 383 $(M + H)^+$

Preparation 64

To a mixture of 3-phenyl-4-pyrazolecarbaldehyde (5.0 g), powder potassium carbonate (4.2 g) and dry N,N-dimethylformamide (50 ml) was added dropwise 4-methoxybenzyl chloride (4.14 ml) with stirring at room temperature. After stirring for 16 hours, the mixture was partitioned between ethyl acetate and water. The separated organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo to give a mixture of 1-(4-methoxybenzyl)-3-phenyl-4-pyrazolecarbaldehyde and 1-(4-methoxybenzyl)-5-phenyl-4-pyrazolecarbaldehyde (9.14 g) as an oil.

IR (Film) : 1670, 1605, 1580, 1510 cm^{-1}

NMR ($CDCl_3$, δ) : 3.77, 3.81(total 3H, each s), 5.18, 5.29(total 2H, each s), 6.78-6.97(2H, m), 7.25-7.74(7H, m), 7.88, 8.10(total 1H, each s), 9.59, 9.91(total 1H, each s)

(+)-APCI/MS : 293 $(M + H)^+$

Preparation 65

4-(1-Hydroxyethyl)-1-(4-methoxybenzyl)-3-phenylpyrazole (1) and 4-(1-hydroxyethyl)-1-(4-methoxybenzyl)-5-phenylpyrazole (2) were obtained in a manner similar to that of Preparation 75.

(1) mp : 97-98°C (AcOEt : n-hexane)

IR (Nujol) : 3340, 1605, 1580, 1540, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 1.47(3H, d, J=6.5Hz), 1.74(1H, broad s),
3.80(3H, s), 5.03(1H, q, J=6.5Hz), 5.24(2H, s),
6.85-6.92(2H, m), 7.23-7.46(6H, m), 7.68-7.75(2H, m)

Analysis Calcd. for $C_{19}H_{20}N_2O_2$:
C 74.00, H 6.54, N 9.08
Found : C 74.10, H 6.53, N 8.95

(+)-APCI/MS : 309 $(M + H)^+$

(2) oil

IR (Film) : 3320, 1610, 1580, 1550, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 1.45(3H, d, J=6.5Hz), 1.71(1H, s),
3.75(3H, s), 4.69(1H, q, J=6.5Hz), 5.11(2H, s),
6.74-6.79(2H, m), 6.94(2H, d, J=8.6Hz), 7.23-7.28(2H, m),
7.40-7.44(3H, m), 7.70(1H, s)

(+)-APCI/MS : 309 $(M + H)^+$

Preparation 66

A mixture of 4-(1-hydroxyethyl)-1-(4-methoxybenzyl)-5-phenylpyrazole, manganese dioxide (5.56 g) and ethyl acetate was stirred for 6 hours at room temperature. The manganese dioxide was filtered off and then the filtrate was evaporated in vacuo to give 4-acetyl-1-(4-methoxybenzyl)-5-phenylpyrazole (1.04 g) as an oil.

IR (Film) : 1680, 1610, 1580, 1535, 1510 cm^{-1}

NMR ($CDCl_3$, δ) : 2.13(3H, s), 3.77(3H, s), 5.05(2H, s),
6.75-6.80(2H, m), 6.92-6.96(2H, m), 7.23-7.28(2H, m),
7.41-7.49(3H, m), 8.04(1H, s)

(+)-APCI/MS : 307 $(M + H)^+$

Preparation 67

4-Acetyl-1-(4-methoxybenzyl)-3-phenylpyrazole was obtained in a

manner similar to that of Preparation 66.

oil

IR (Film) : 1660, 1605, 1580, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 2.25(3H, s), 3.81(3H, s), 5.26(2H, s), 6.88-6.95(2H, m), 7.27-7.31(2H, m), 7.37-7.47(3H, m), 7.62-7.80(2H, m), 7.86(1H, s)

(+)-APCI/MS : 307 $(M + H)^+$

Preparation 68

3,4-Diphenyl-1-(4-methoxybenzyl)pyrazole was obtained in a manner similar to that of Preparation 9.

oil

IR (Nujol) : 1600, 1580, 1540, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 3.80(3H, s), 5.30(2H, s), 6.90(2H, d, J=8.5Hz), 7.16-7.37(10H, m), 7.49-7.53(2H, m)

(+)-APCI/MS : 341 $(M + H)^+$

Preparation 69

To a mixture of 3,4-diphenyl-1-(4-methoxybenzyl)pyrazole (1.0 g), tetrahydrofuran (15 ml) and diethyl ether (10 ml) was added dropwise 1.64M n-butyl lithium in n-hexane (2.2 ml) with stirring at below -68 ℃ under nitrogen atmosphere. After stirring for 1.5 hours under the same conditions, dry N,N-dimethylformamide (0.25 ml) was added to the mixture and then the mixture was stirred for 4.5 hours at below -70 ℃. This mixture was treated with aqueous saturated ammonium hydrochloride and warmed up to room temperature. The mixture was partitioned between etheyl acetate and water. The separated organic layer was evaporated. The residue was chromatographed on silica gel

(40 ml) using a mixture of ethyl acetate and n-hexane (8:1) to give 0.41 g of a crude product as a solid, which was recrystallized from a mixture of ethyl acetate and n-hexane to give 3,4-diphenyl-5-formyl-1-(4-methoxybenzyl)pyrazole (0.29 g).

mp : 135-136°C

IR (Nujol) : 1675, 1615, 1510 cm^{-1}

NMR ($CDCl_3$, δ) : 3.77(3H, s), 5.75(2H, s),
6.82-6.89(12H, m), 9.59(1H, s)

Analysis Calcd. for $C_{24}H_{20}N_2O_2$:
C 78.24, H 5.47, N 7.60
Found : C 78.35, H 5.58, N 7.68

(+)-APCI/MS : 369 $(M + H)^+$

Preparation 70

3,4-Diphenyl-5-(1-hydroxyethyl)-1-(4-methoxybenzyl)pyrazole was obtained in a manner similar to that of Preparation 75.

IR (Nujol) : 3250, 1600, 1575, 1510, 1500 cm^{-1}

NMR ($CDCl_3$, δ) : 1.35(3H, d, J=6.8Hz), 3.77(3H, s),
4.97(1H, q, J=6.8Hz), 5.50(1H, d, J=15.5Hz),
5.60(1H, d, J=15.5Hz), 6.83-6.89(2H, m), 7.17-7.42(12H, m)

(+)-APCI/MS : 385 $(M + H)^+$

Preparation 71

To a solution of 3,4-diphenyl-5-(1-hydroxyethyl)-1-(4-methoxybenzyl)pyrazole (2.27 g) and triethylamine (1.6 ml) in dimethylsulfoxide (23 ml) was added sulfur trioxide pyridine complex (0.94 g) with stirring at room temperature. After stirring for 5 days, the mixture was partitioned between ethyl acetate and water. The separated organic layer was washed with water, dried over

magnesium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (100 ml) using a mixture of ethyl acetate and n-hexane (6:1). The desired fractions were collected and evaporated in vacuo. The residue was recrystallized from a mixture of ethyl acetate and n-hexane to give 5-acetyl-3,4-diphenyl-1-(4-methoxybenzyl)pyrazole (1.11 g).

mp : 110-111℃

IR (Nujol) : 1660, 1605, 1585, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 1.88(3H, s), 3.77(3H, s), 5.70(2H, s), 6.82-6.88(2H, m), 7.19-7.41(12H, m)

Analysis Calcd. for $C_{25}H_{22}N_2O_2$:

C 78.51, H 5.80, N 7.32

Found : C 78.09, H 5.83, N 7.32

(+)-APCI/MS : 383 $(M + H)^+$

Preparation 72

To a mixture of methyl 3-phenyl-5-pyrazolecarboxylate (7.94 g), potassium tert-butoxide (4.41 g), 18-crown-6 (1.04 g) and dry tetrahydrofuran (80 ml) was added 4-methoxybenzyl chloride (5.33 ml) at room temperature. After the mixture was stirred at room temperature for 8 days, it was poured into dil. hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and brine, dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography on SiO_2 using a mixture of n-hexane and ethyl acetate (6:1) to give 8.25 g of methyl 1-(4-methoxybenzyl)-3-phenyl-5-pyrazolecarboxylate as crystals.

mp : 71-72℃ (AcOEt : n-hexane)

IR (Nujol) : 1720, 1605, 1580, 1500 cm^{-1}

NMR ($CDCl_3$, δ) : 3.76(3H, s), 3.86(3H, s), 5.73(2H, s), 6.78-6.86(2H, m), 7.25(1H, s), 7.27-7.45(5H, m), 7.80-7.85(2H, m)

Analysis Calcd. for $C_{19}H_{18}N_2O_3$:

C 70.79, H 5.63, N 8.67

Found : C 70.80, H 5.63, N 8.63

Preparation 73

To a mixture of methyl 1-(4-methoxybenzyl)-3-phenyl-5-pyrazolecarboxylate (8.44 g) and methanol (90 ml) was added 1N sodium hydroxide solution in water (34 ml) with stirring at room temperature. The mixture was refluxed for 0.25 hour and evaporated in vacuo. The residue was dissolved in water, which mixture was acidified with aqueous hydrochloric acid. The resulting solid was collected by filtration to give 1-(4-methoxybenzyl)-3-phenyl-5-pyrazolecarboxylic acid (7.20 g).

NMR (DMSO-d_6, δ) : 3.71(3H, s), 5.70(2H, s), 6.88(2H, d, J=8.4Hz), 7.19(2H, d, J=8.4Hz), 7.34-7.45(4H, m), 7.86(2H, d, J=7.0Hz)

(+)-APCI/MS : 309 $(M + H)^+$

Preparation 74

To a solution of 1-(4-methoxybenzyl)-3-phenyl-5-pyrazolecarboxylic acid (0.48 g), N,O-dimethylhydroxylamine hydrochloride (0.15 g), 1-hydroxybenzotriazole (0.23 g) and 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide hydrochloride (0.33 g) in dry dimethylformamide (5 ml) was added triethylamine (0.48 ml) at room temperature. After stirring for 1 hour, the mixture was partitioned between water and

ethyl acetate. The separated organic layer was dried over magnesium sulfate and evaporated in vacuo to give 5-(N-methyl-N-methoxycarbamoyl)-1-(4-methoxybenzyl)-3-phenylpyrazole (0.48 g) as an oil.

NMR ($CDCl_3$, δ) : 3.28(3H, s), 3.43(3H, s), 3.75(3H, s), 5.66(2H, s), 6.78-6.84(2H, m), 7.01(1H, s), 7.26-7.45(5H, m), 7.81-7.85(2H, m)

(+)-APCI/MS : 352 $(M + H)^+$

Preparation 75

3M-Methylmagnesium bromide in tetrahydrofuran (23.7 ml) was added dropwise to a solution of 5-(N-methyl-N-methoxycarbamoyl)-1-(4-methoxybenzyl)-3-phenylpyrazole (8.3 g) in dry tetrahydrofuran (125 ml) with stirring at below 5°C under nitrogen atmosphere. The reaction mixture was stirred for 0.5 hour under the same conditions. The reaction mixture was treated with saturated aqueous Rochelle salt. The precipitates were filtered off and then the filtrate was evaporated in vacuo. The residue was chromatographed on silica gel (160 ml) using a mixture of ethyl acetate and n-hexane. The desired fractions were collected and evaporated in vacuo. The residue was recrystallized from a mixture of ethyl acetate and n-hexane to give 5-acetyl-1-(4-methoxybenzyl)-3-phenylpyrazole (4.88 g).

mp : 79-80°C (AcOEt : n-hexane)

IR (Nujol) : 1670, 1600, 1580, 1500 cm^{-1}

NMR ($CDCl_3$, δ) : 2.51(3H, s), 3.75(3H, s), 5.71(2H, s), 6.77-6.84(2H, m), 7.10(1H, s), 7.24-7.46(5H, m), 7.80-7.85(2H, m)

Analysis Calcd. for $C_{19}H_{18}N_2O_2 \cdot 1/4H_2O$:

C 73.41, H 6.00, N 9.01

Found : C 73.82, H 5.89, N 9.02

(+)-APCI/MS : 307 $(M + H)^+$

Preparation 76

A mixture of 4-acetyl-3-(3-methoxyphenyl)-5-phenylpyrazole (0.1 g) and 48% aqueous hydrogen bromide (1 ml) was refluxed with stirring for 3 hours. To the reaction mixture was added water, and the resulting mixture was extracted with ethyl acetate. The separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was recrystallized from a mixture of ethyl acetate and n-hexane to give 4-acetyl-3-(3-hydroxyphenyl)-5-phenylpyrazole (50 mg).

mp : 179-180℃

IR (Nujol) : 3350, 3150, 1650, 1580 cm^{-1}

NMR (DMSO-d_6, δ) : 2.08(3H, s), 6.70-7.00(3H, m), 7.10-7.55(6H, m), 9.55, 9.74(total 1H, each s), 13.53(1H, s)

Analysis Calcd. for $C_{17}H_{14}N_2O_2 \cdot H_2O$:

C 68.91, H 5.44, N 9.45

Found : C 68.65, H 5.27, N 9.32

(+)-APCI/MS : 279 $(M + H)^+$

Preparation 77

To a mixture of 4-acetyl-3-(3-hydroxyphenyl)-5-phenylpyrazole (0.28 g), imidazole (0.23 g) and dry tetrahydrofuran (6 ml) was added dropwise t-butyldimethylsilyl chloride (0.24 g) at room temperature. After stirring for 4.5 hours, water was added to the reaction mixture. The mixture was extracted with ethyl acetate and the extract was washed with water. The solvent was evaporated in vacuo. The residue

was chromatographed on silica gel (30 ml) using a mixture of ethyl acetate and n-hexane (1:4) to give 4-acetyl-3-(3-t-butyldimethylsilyloxyphenyl)-5-phenylpyrazole (0.31 g) as an oil.

NMR (DMSO-d_6, δ) : 0.22(6H, s), 0.98(9H, s), 2.06(3H, s), 6.90-7.00(1H, m), 7.05(1H, t, J=1.7Hz), 7.16(1H, d, J=7.77Hz), 7.30-7.57(6H, m), 13.59(1H, s)

(+)-APCI/MS : 393 $(M + H)^+$

Preparation 78

To a mixture of 4-acetyl-3-(3-t-butyldimethylsilyloxyphenyl)-5-phenylpyrazole (0.22 g), 4-methoxybenzyl alcohol (0.105 ml), triphenylphosphine (0.22 g) and dry tetrahydrofuran (3.3 ml) was added dropwise diethyl azodicarboxylate (0.13 ml) under ice-cooling. After stirring for 1 hour, the mixture was poured into water and the mixture was extracted with ethyl acetate. The extract was washed with water and evaporated in vacuo. The residue was chromatographed on silica gel (20 ml) using a mixture of chloroform and n-hexane (3:1) to give a mixture of 4-acetyl-3-(3-t-butyldimethylsilyloxyphenyl)-1-(4-methoxybenzyl)-5-phenylpyrazole and 4-acetyl-5-(3-t-butyldimethylsilyloxyphenyl)-1-(4-methoxybenzyl)-3-phenylpyrazole (0.19 g) as an oil.

IR (Film) : 1670, 1605, 1580, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 0.18, 0.24(total 6H, each s), 0.96, 0.99(total 9H, each s), 1.90, 1.93(total 3H, each s), 3.73(3H, s), 5.12, 5.14(total 2H, each s), 6.59-7.37(13H, m)

(+)-APCI/MS : 513 $(M + H)^+$

Preparation 79

1M-Tetrabutylammonium fluoride solution in tetrahydrofuran (9.85

ml) was added dropwise to solution of 4-acetyl-3-(3-t-butyldimethylsilyloxyphenyl)-1-(4-methoxybenzyl)-5-phenylpyrazole and 4-acetyl-5-(3-t-butyldimethylsilyloxyphenyl)-1-(4-methoxybenzyl)-3-phenylpyrazole (3.88 g) in dry tetrahydrofuran (10 ml) with stirring under ice-cooling. After stirring for 0.5 hour, the solution was evaporated in vacuo. The residue was chromatographed on silica gel (80 ml) using a mixture of ethyl acetate and n-hexane to give 2.86 g of a crude product as an oil, which was recrystallized from a mixture of ethyl ether and petroleum ether to give 4-acetyl-3-(3-hydroxyphenyl)-1-(4-methoxybenzyl)-5-phenylpyrazole (1.28 g) as crystals.

mp : 127-128℃

IR (Nujol) : 1660, 1600, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 1.91(3H, s), 3.70(3H, s), 5.09(2H, s), 6.77-7.00(7H, m), 7.30-7.57(6H, m), 9.79(1H, broad s)

Analysis Calcd. for $C_{25}H_{22}N_2O_3 \cdot 1/4H_2O$:

C 74.52, H 5.63, N 6.95

Found : C 74.67, H 5.49, N 6.90

(+)-APCI/MS : 399 $(M + H)^+$

Preparation 80

To a mixture of 4-acetyl-3-(3-hydroxyphenyl)-1-(4-methoxybenzyl)-5-phenylpyrazole (0.50 g), 2-phenylethyl alcohol (0.24 ml), triphenylphosphine (0.53 g) and tetrahydrofuran (5 ml) was added diethyl azodicarboxylate (0.32 ml) under ice-cooling. The mixture was stirred at room temperature for 6 hours. Solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel using a mixture of n-hexane and ethyl acetate (5:1) as an eluent to give 4-acetyl-1-(4-methoxybenzyl)-5-

phenyl-3-[3-(2-phenylethoxy)phenyl]pyrazole as an oil (0.63 g).

IR (Film) : 1710, 1670, 1610, 1585, 1515 cm^{-1}

NMR (DMSO-d_6, δ) : 1.89(3H, s), 3.02(2H, t, J=6.3Hz), 3.68(3H, s), 4.18(2H, t, J=6.3Hz), 5.09(2H, s), 6.79-7.59(18H, m)

(+)-APCI/MS : 503 $(M + H)^+$

Preparation 81

Trifluoromethanesulfonic anhydride (0.27 ml) was added dropwise to a mixture of 4-acetyl-3-(3-hydroxyphenyl)-5-phenylpyrazole, triethylamine (0.50 ml) and dry 1,2-dichloroethane (4 ml) at below 10℃ under nitrogen atmosphere. The mixture was warmed up to room temperature and stirred for 18 hours. The mixture was partitioned between water and chloroform. The separated organic layer was evaporated in vacuo. The residue was chromatographed on silica gel (40 ml) using a mixture of ethyl acetate and n-hexane (1:3) to give an oil (0.21 g), which was recrystallized from a mixture of ethyl acetate and n-hexane to give 4-acetyl-5-phenyl-3-(3-trifluoromethanesulfonyloxyphenyl)pyrazole (0.17 g).

mp : 135-136℃

IR (Nujol) : 3160, 3080, 1630, 1570 cm^{-1}

NMR (DMSO-d_6, δ) : 2.05(3H, s), 7.50-7.77(9H, m), 13.79(1H, s)

Analysis Calcd. for $C_{18}H_{13}F_3N_2O_4S \cdot 1/10$ n-hexane :

C 53.32, H 3.46, N 6.69

Found : C 53.22, H 3.13, N 6.84

(+)-APCI/MS : 411 $(M + H)^+$

Preparation 82

A mixture of 4-acetyl-5-phenyl-3-(3-trifluoromethanesulfonyl-

oxyphenyl)pyrazole (0.58 g), 3-trifluoromethylphenylboric acid (0.51 g), tetrakis(triphenylphosphine)palladium (0) (49 mg), triethylamine (0.76 ml) and dry N,N-dimethylformamide (6.1 ml) was heated with stirring at 100℃ for 8 hours under nitrogen atmosphere. The mixture was partitioned between water and ethyl acetate. The separated organic layer was washed with aqueous sodium bicarbonate and evaporated in vacuo. The residue was chromatographed on silica gel using a mixture of toluene and acetone (20:1) to give 4-acetyl-5-phenyl-3-[3-(3-trifluoromethylphenyl)phenyl]pyrazole (0.40 g) as an oil.

IR (Film) : 1660, 1595 cm^{-1}

NMR (DMSO-d_6, δ) : 2.08(3H, s), 7.03-7.25(2H, m), 7.40-7.90(9H, m), 7.95-8.15(2H, m), 13.69(1H, s)

(+)-APCI/MS : 407 $(M + H)^+$

Example 1

A mixture of 4-acetyl-3,5-diphenyl-1-methylpyrazole (1.0 g), glyoxylic acid monohydrate (0.67 g) and 1,2-dimethoxyethane (3 ml) was refluxed for 26 hours. The solvent was evaporated in vacuo. To the residue was added 80%-hydrazine monohydrate (2.2 ml) and then the mixture was heated with stirring at 125℃ for 2 hours. Ethanol was added and then the resulting solid was collected by filtration to give 3,5-diphenyl-1-methyl-4-(3-oxo-2,3-dihydropyridazin-6-yl)-pyrazole (0.62 g). The solid (0.25 g) was recrystallized from ethanol to give the object compound (0.208 g) as white crystals.

mp : above 270℃

IR (Nujol) : 1670, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 3.82 (3H, s), 6.73 (1H, d, J=9.7Hz),
7.00 (1H, d, J=9.7Hz), 7.31-7.50 (10H, m)

Analysis Calcd. for $C_{20}H_{16}N_4O \cdot 1/2H_2O$:
C 71.20, H 5.08, N 16.61
Found : C 70.98, H 5.09, N 16.53

(+)-APCI/MS : 329 ($M^+ + 1$)

The following compounds (Examples 2 to 4) were obtained according to a manner similar to that of Example 1.

Example 2

5-(Furan-2-yl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-3-phenylpyrazole

mp : >270℃ (DMF : H_2O)

IR (Nujol) : 1645, 1580 cm^{-1}

NMR (DMSO-d_6, δ) : 6.95-7.10 (3H, m), 7.18 (1H, d, J=3.6Hz),
7.36-7.47 (3H, m), 7.83-7.99 (3H, m), 13.16 (1H, m),
13.55 (1H, s)

Analysis Calcd. for $C_{17}H_{12}N_4O_2 \cdot 1/2H_2O \cdot 1/10DMF$:
C 64.80, H 4.30, N 17.91
Found : C 64.48, H 4.01, N 18.18

(+)-APCI/MS : 305 ($M^+ + 1$)

Example 3

1-Benzyl-3,5-diphenyl-4-(3-oxo-2,3-dihydropyridazin-6-yl)pyrazole

mp : 229-231℃ (AcOEt)

IR (Nujol) : 1670, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 5.33 (2H, s), 6.72 (1H, d, J=9.7Hz),
7.01-7.51 (16H, m), 12.99 (1H, s),

Analysis Calcd. for $C_{26}H_{20}N_4O \cdot 1/4H_2O$:

C 76.36, H 5.05, N 13.70

Found : C 76.48, H 5.01, N 13.97

(+)-APCI/MS : 405 (M^+ + 1)

Example 4

3,5-Diphenyl-4-(3-oxo-2,3-dihydropyridazin-6-yl)-1-(phenethyl)-pyrazole

mp : 203-204℃ (AcOEt)

IR (Nujol) : 1645, 1585 cm^{-1}

NMR (DMSO-d_6, δ) : 3.10 (2H, t, J=7.0Hz),
4.24 (2H, t, J=7.0Hz), 6.70 (1H, d, J=9.7Hz),
6.94 (1H, d, J=9.7Hz), 6.96-7.00 (2H, m), 7.07-7.12 (2H, m),
7.20-7.24 (3H, m), 7.33-7.52 (8H, m), 12.94 (1H, s)

Analysis Calcd. for $C_{27}H_{22}N_4O \cdot 0.3\text{-AcOEt} \cdot 0.3\text{-}H_2O$:

C 75.21, H 5.60, N 12.44

Found : C 75.23, H 5.53, N 12.33

(+)-APCI/MS : 419 (M^+ + 1)

Example 5

A solution of 1-benzyl-3,5-diphenyl-4-(3-oxo-2,3-dihydropyridazin-6-yl)pyrazole (1.52 g) in dry tetrahydrofuran (80 ml) was added dropwise to a solution of sodium (0.95 g) in liquid ammonia (about 100 ml) over a period of 10 minutes at below -70℃ under nitrogen atmosphere. After stirring for 1 hour under the same conditions, the reaction mixture was warmed up to room temperature. The mixture was treated with ethanol (5 ml), acidified with 1N-hydrochloric acid, and extracted with ethyl acetate. The separated organic layer was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was recrystallized from ethanol to give 3,5-diphenyl-4-

(3-oxo-2,3-dihydropyridazin-6-yl)pyrazole (0.61 g).

mp : >260℃

IR (Nujol) : 3150, 1670, 1590, 1530 cm^{-1}

NMR (DMSO-d_6, δ) : 6.82 (1H, d, J=9.7Hz),
7.14 (1H, d, J=9.7Hz), 7.32-7.62 (11H, m), 13.09 (1H, s)

Analysis Calcd. for $C_{19}H_{14}N_4O \cdot EtOH$:
C 69.98, H 5.59, N 15.54
Found : C 69.71, H 5.33, N 15.95

(+)-APCI/MS : 315 $(M^+ + 1)$

The following compounds (Examples 6 to 8) were obtained according to a manner similar to that of Example 1.

Example 6

3-(3-Methoxyphenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenylpyrazole

mp : 207-208℃ (EtOH : H_2O)

IR (Nujol) : 1670, 1585 cm^{-1}

NMR (DMSO-d_6, δ) : 3.74 (3H, s), 6.84 (1H, d, J=9.8Hz),
6.90-7.10 (3H, m), 7.15 (1H, d, J=9.8Hz),
7.20-7.50 (6H, m), 13.13 (1H, s), 13.60 (1H, s)

Analysis Calcd. for $C_{20}H_{16}N_4O_2 \cdot 1.1H_2O$:
C 68.99, H 5.26, N 60.09
Found : C 68.67, H 4.73, N 60.07

(+)-APCI/MS : 345 $(M + H)^+$

Example 7

3-(3-Methylphenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenylpyrazole

mp : 249-252℃ (EtOH : H_2O)

IR (Nujol) : 1670, 1590, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.31 (3H, s), 6.82 (1H, d, J=9.7Hz), 7.12 (1H, d, J=9.7Hz), 7.19-7.50 (9H, m), 13.09 (1H, s), 13.56 (1H, s)

Analysis Calcd. for $C_{20}H_{16}N_4O \cdot 1/2H_2O$:

C 71.20, H 5.08, N 16.61

Found : C 71.41, H 5.00, N 16.75

(+)-APCI/MS : 328 $(M + H)^+$

Example 8

3-(3-Chlorophenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenylpyrazole

mp : 211-213℃ (EtOH : H_2O)

IR (Nujol) : 1680, 1595, 1545 cm^{-1}

NMR (DMSO-d_6, δ) : 6.85 (1H, d, J=9.7Hz), 7.16 (1H, d, J=9.7Hz), 7.13-7.54 (9H, m), 13.14 (1H, s), 13.72 (1H, s)

Analysis Calcd. for $C_{19}H_{13}ClN_4O$:

C 65.43, H 3.76, N 16.06

Found : C 65.09, H 3.67, N 16.12

(+)-APCI/MS : 349 $(M + H)^+$, 351 $(M + H)^+$

Example 9

3-(3-Fluorophenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenylpyrazole was obtained in a manner similar to that of Example 1.

mp : 259-262℃ (EtOH : H_2O)

IR (Nujol) : 3150, 1670, 1590, 1530 cm^{-1}

NMR (DMSO-d_6, δ) : 6.83(1H, d, J=9.7Hz), 7.14(1H, d, J=9.7Hz), 7.24-7.44(9H, m), 13.12(1H, s), 13.67(1H, s)

Analysis Calcd. for $C_{19}H_{13}FN_4O \cdot 1.6H_2O$:

C 63.19, H 4.52, N 15.51

Found : C 63.02, H 4.49, N 15.38

(+)-APCI/MS : 333 $(M + H)^+$

Example 10

3-(2-Chlorophenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenylpyrazole was obtained in a manner similar to that of Example 1.

mp : 242-244℃ (EtOH : H_2O)

IR (Nujol) : 3200, 1650, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 6.74(1H, d, J=9.8Hz), 6.93(1H, d, J=9.8Hz), 7.30-7.70(9H, m), 12.88(1H, s), 13.55, 13.66(total 1H, each s)

Analysis Calcd. for $C_{19}H_{13}ClN_4O \cdot 1/4H_2O$:

C 64.60, H 3.85, N 15.86

Found : C 64.63, H 3.86, N 15.98

(+)-APCI/MS : 349 $(M + H)^+$

Example 11

3-(4-Chlorophenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenylpyrazole was obtained in a manner similar to that of Example 1.

mp : >260℃ ($CHCl_3$: AcOEt)

IR (Nujol) : 1670, 1595, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 6.83(1H, d, J=9.7Hz), 7.12(1H, d, J=9.7Hz), 7.43-7.48(9H, m)

Analysis Calcd. for $C_{19}H_{13}ClN_4O$:

C 65.43, H 3.76, N 16.06

Found : C 65.55, H 3.79, N 15.83

(+)-APCI/MS : 349 $(M + H)^+$

Example 12

3-(3,4-Dichlorophenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenylpyrazole was obtained in a manner similar to that of Example 1.

mp : 231-233℃

IR (Nujol) : 1680, 1650, 1590, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 6.84(1H, d, J=9.7Hz), 7.14(1H, d, J=9.7Hz), 7.30-7.73(8H, m), 13.13(1H, s), 13.75(1H, s)

Analysis Calcd. for $C_{19}H_{12}Cl_2N_4O \cdot 1/2H_2O$:

C 58.20, H 3.34, N 14.28

Found : C 58.40, H 3.07, N 14.45

(+)-APCI/MS : 383 $(M + H)^+$

Example 13

3-(3,5-Dichlorophenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenylpyrazole was obtained in a manner similar to that of Example 1.

mp : 163-164℃ (EtOH)

IR (Nujol) : 3150, 3100, 1675, 1595, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 6.86(1H, d, J=9.7Hz), 7.17(1H, d, J=9.7Hz), 7.43-7.68(8H, m)

Analysis Calcd. for $C_{19}H_{12}Cl_2N_4O \cdot 1/2EtOH$:

C 56.62, H 4.04, N 13.20

Found : C 57.03, H 4.03, N 12.98

(+)-APCI/MS : 383 $(M + H)^+$

Example 14

3-(2-Methylphenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenylpyrazole was obtained in a manner similar to that of Example 1.

mp : >250℃ (EtOH : H_2O)

IR (Nujol) : 3200, 1650, 1590, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 2.13(3H, s), 6.72 (1H, d, J=9.7Hz),
6.96(1H, d, J=9.7Hz), 6.93-7.52(9H, m), 12.94(9H, s),
13.55, 13.56(total 1H, each s)

Analysis Calcd. for $C_{20}H_{16}N_4O \cdot 1/4H_2O$:
C 72.16, H 4.99, N 16.83
Found : C 72.15, H 4.97, N 16.95

(+)-APCI/MS : 329 $(M + H)^+$

Example 15

3-(4-Methylphenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenylpyrazole was obtained in a manner similar to that of Example 1.

mp : 259-261℃ (EtOH : H_2O)

IR (Nujol) : 1675, 1590, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.32(3H, s), 6.82(1H, d, J=9.7Hz),
7.11(1H, d, J=9.7Hz), 7.14-7.44(9H, m), 13.09(1H, s),
13.57(1H, s)

Analysis Calcd. for $C_{20}H_{16}N_4O \cdot 1/3EtOH$:
C 71.98, H 5.27, N 16.30
Found : C 72.24, H 4.97, N 16.11

(+)-APCI/MS : 329 $(M + H)^+$

Example 16

3-(3-Ethylphenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenylpyrazole was obtained in a manner similar to that of Example 1.

mp : 211-213℃ (EtOH : H_2O)

IR (Nujol) : 1680, 1595, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 1.15(3H, t, J=7.5Hz), 2.59(2H, q, J=7.5Hz),
6.81(1H, d, J=9.7Hz), 7.13(1H, d, J=9.7Hz),
7.15-7.45(9H, m), 13.08(1H, s), 13.54(1H, s)

Analysis Calcd. for $C_{21}H_{18}N_4O \cdot 1/3EtOH$:

C 72.74, H 5.63, N 15.66

Found : C 73.12, H 5.47, N 15.30

(+)-APCI/MS : 342 $(M + H)^+$

Example 17

3-(4-Methoxyphenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenylpyrazole was obtained in a manner similar to that of Example 1.

mp : 215-218℃ (EtOH : H_2O)

IR (Nujol) : 1680, 1600, 1540, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 3.77(3H, s), 6.82(1H, d, J=9.7Hz), 6.85-7.09(2H, m), 7.06(1H, d, J=9.7Hz), 7.35-7.44(7H, m), 13.08(1H, s), 13.46(1H, s)

Analysis Calcd. for $C_{20}H_{16}N_4O_2 \cdot 1/4H_2O$:

C 68.86, H 4.77, N 16.06

Found : C 68.61, H 4.69, N 15.97

(+)-APCI/MS : 345 $(M + H)^+$

Example 18

3-(3-Ethoxyphenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenylpyrazole was obtained in a manner similar to that of Example 1.

mp : 214-215℃ (EtOH : H_2O)

IR (Nujol) : 1680, 1590, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 1.31(3H, t, J=6.9Hz), 3.90-4.10(2H, m), 6.83(1H, d, J=9.8Hz), 6.86-7.02(3H, m), 7.14(1H, d, J=9.8Hz), 7.17-7.44(6H, m), 13.11(1H, s), 13.57(1H, s)

Analysis Calcd. for $C_{21}H_{18}N_4O_2 \cdot 0.18M\text{-}CHCl_3$:

C 66.97, H 4.82, N 14.75

Found : C 67.16, H 4.79, N 14.25

(+)-APCI/MS : 359 $(M + H)^+$

Example 19

3-(3-Isopropoxyphenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenylpyrazole was obtained in a manner similar to that of Example 1.

mp : 183-185℃ (AcOEt : n-hexane)

IR (Nujol) : 1680, 1595 cm^{-1}

NMR (DMSO-d_6, δ) : 1.24(6H, d, J=6.0Hz), 4.54(1H, broad s), 6.84(1H, d, J=9.7Hz), 6.86-7.14(3H, m), 7.16(1H, d, J=9.7Hz), 7.19-7.44(6H, m), 13.12(1H, s), 13.56(1H, s)

Analysis Calcd. for $C_{22}H_{20}N_4O_2$:

C 70.95, H 5.41, N 15.04

Found : C 71.14, H 5.32, N 15.04

(+)-APCI/MS : 373 $(M + H)^+$

Example 20

3,5-Bis(3-chlorophenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-pyrazole was obtained in a manner similar to that of Example 1.

mp : 240-242℃ (EtOH : H_2O)

IR (Nujol) : 1690, 1595 cm^{-1}

NMR (DMSO-d_6, δ) : 6.87(1H, d, J=9.7Hz), 7.18(1H, d, J=9.7Hz), 7.33-7.54(8H, m), 13.19(1H, s), 13.83(1H, s)

Analysis Calcd. for $C_{19}H_{12}Cl_2N_4O \cdot 1/3EtOH$:

C 59.26, H 3.54, N 14.06

Found : C 59.64, H 3.51, N 13.75

(+)-APCI/MS : 383 $(M + H)^+$

Example 21

3,5-Bis(4-methoxyphenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-pyrazole was obtained in a manner similar to that of Example 1.

mp : >250℃ (EtOH : H_2O)

IR (Nujol) : 1680, 1600, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 3.76(6H, s), 6.81(1H, d, J=9.8Hz),
6.84-7.09(4H, m), 7.10(1H, d, J=9.8Hz),
7.37(4H, d, J=8.7Hz), 13.08(1H, s), 13.35(1H, s)

Analysis Calcd. for $C_{21}H_{18}N_4O_3 \cdot 1/4H_2O$:
C 66.57, H 4.92, N 14.79
Found : C 66.21, H 4.85, N 14.82

(+)-APCI/MS : 375 $(M + H)^+$

Example 22

4-(3-Oxo-2,3-dihydropyridazin-6-yl)-5-phenyl-3-[3-(3-trifluoromethylphenyl)phenyl]pyrazole was obtained in a manner similar to that of Example 1.

mp : 115-116℃ (EtOH : H_2O)

IR (Nujol) : 1680, 1590, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 6.86(1H, d, J=9.8Hz),
7.20(1H, d, J=9.8Hz), 7.30-8.10(13H, m), 13.12(1H, s),
13.65, 13.70(total 1H, each s)

(+)-APCI/MS : 459 $(M + H)^+$

Example 23

3,5-Diphenyl-1-ethyl-4-(3-oxo-2,3-dihydropyridazin-6-yl)-pyrazole was obtained in a manner similar to that of Example 1.

mp : 214-216℃ (EtOH : H_2O)

IR (Nujol) : 1645, 1580 cm^{-1}

NMR (DMSO-d_6, δ) : 1.34(3H, t, J=7.2Hz),

4.08(2H, q, J=7.2Hz), 6.71(1H, d, J=9.7Hz),
7.00(1H, d, J=9.7Hz), 7.29-7.50(10H, m), 12.96(1H, s)

Analysis Calcd. for $C_{21}H_{18}N_4O \cdot 1/4H_2O$:
C 72.71, H 5.38, N 16.15
Found : C 73.09, H 5.33, N 16.27

(+)-APCI/MS : 343 $(M + H)^+$

Example 24

1-Isobutyl-3,5-diphenyl-4-(3-oxo-2,3-dihydropyridazin-6-yl)-pyrazole was obtained in a manner similar to that of Example 1.

mp : 186-187℃ (AcOEt : n-hexane)

IR (Nujol) : 1670, 1590 cm^{-1}

NMR ($CDCl_3$, δ) : 0.81(6H, d, J=6.7Hz), 2.17-2.40(1H, m),
3.90(2H, d, J=7.4Hz), 6.68(1H, d, J=9.7Hz),
7.86(1H, d, J=9.7Hz), 7.31-7.55(10H, m), 10.94(1H, s)

Analysis Calcd. for $C_{23}H_{22}N_4O \cdot 1/6AcOEt \cdot 1/5n\text{-hexane}$:
C 74.23, H 6.61, N 13.93
Found : C 74.60, H 6.71, N 14.03

(+)-APCI/MS : 371 $(M + H)^+$

Example 25

3,5-Diphenyl-4-(3-oxo-2,3-dihydropyridazin-6-yl)-1-n-pentylpyrazole was obtained in a manner similar to that of Example 1.

mp : 160-161℃ (EtOH : H_2O)

IR (Nujol) : 1645, 1585 cm^{-1}

NMR (DMSO-d_6, δ) : 0.78(3H, t, J=6.5Hz), 1.12-1.19(4H, m),
1.60-1.85(2H, m), 4.05(2H, t, J=7.3Hz),
6.70(1H, d, J=9.8Hz), 7.00(1H, d, J=9.8Hz),
7.29-7.49(10H, m), 12.96(1H, s)

Analysis Calcd. for $C_{24}H_{24}N_4O \cdot 1/4H_2O$:

C 74.11, H 6.35, N 14.40

Found : C 74.12, H 6.26, N 14.48

(+)-APCI/MS : 385 $(M + H)^+$

Example 26

1-Benzyl-5-methyl-4-(3-oxo-2,3-dihydropyridazin-6-yl)-3-phenylpyrazole was obtained in a manner similar to that of Example 1.

mp : >250℃ (EtOH : H_2O)

IR (Nujol) : 1670, 1590 cm^{-1}

NMR ($CDCl_3$, δ) : 2.32(3H, s), 5.39(2H, s),
6.78(1H, d, J=9.8Hz), 6.96(1H, d, J=9.8Hz),
7.19-7.51(10H, m), 11.84(1H, s)

Analysis Calcd. for $C_{21}H_{18}N_4O \cdot 1/4H_2O$:

C 72.71, H 5.38, N 16.15

Found : C 72.98, H 5.40, N 16.43

(+)-APCI/MS : 343 $(M + H)^+$

Example 27

1-(4-Methoxybenzyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-3-phenylpyrazole was obtained in a manner similar to that of Example 1.

mp : 153-155℃ (AcOEt : n-hexane)

IR (Nujol) : 1660, 1590, 1550, 1505 cm^{-1}

NMR (DMSO-d_6, δ) : 3.73(3H, s), 5.31(2H, s),
6.82(1H, d, J=9.8Hz), 6.93(2H, d, J=8.6Hz),
7.24(1H, d, J=9.8Hz), 7.26-7.44(7H, m), 8.21(1H, s),
13.00(1H, s)

Analysis Calcd. for $C_{21}H_{18}N_4O_2$:

C 70.38, H 5.06, N 15.63

Found : C 70.37, H 5.07, N 15.49

(+)-APCI/MS : 359 $(M + H)^+$

Example 28

1-(4-Methoxybenzyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenylpyrazole was obtained in a manner similar to that of Example 1.

mp : 203-204°C (AcOEt)

IR (Nujol) : 1650, 1600, 1590, 1505 cm^{-1}

NMR ($CDCl_3$, δ) : 3.76(3H, s), 5.12(2H, s), 6.66-6.86(4H, m), 6.93-6.97(2H, m), 7.20-7.26(2H, m), 7.37-7.51(3H, m), 7.96(1H, s), 11.35(1H, s)

Analysis Calcd. for $C_{21}H_{18}N_4O_2 \cdot 1/4H_2O$:

C 69.50, H 5.14, N 15.44

Found : C 69.44, H 5.21, N 15.05

(+)-APCI/MS : 359 $(M + H)^+$

Example 29

1-(4-Methoxybenzyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenyl-3-[3-(2-phenylethoxy)phenyl]pyrazole was obtained in a manner similar to that of Example 1.

mp : 249-253°C (AcOEt : EtOH)

IR (Nujol) : 1660, 1650, 1590, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 2.95-3.10(2H, m), 3.70(3H, s), 4.10-4.21(2H, m), 5.24(2H, s), 6.68-7.06(9H, m), 7.20-7.46(11H, m), 12.98(1H, s)

Analysis Calcd. for $C_{35}H_{30}N_4O_3 \cdot 1/2H_2O$:

C 74.58, H 5.54, N 9.94

Found : C 74.75, H 5.53, N 9.95

(+)-APCI/MS : 555 $(M + H)^+$

Example 30

A mixture of 4-acetyl-3,5-diphenyl-1-(4-methoxybenzyl)pyrazole (0.73 g), glyoxylic acid monohydrate (0.73 g) and dry 1,2-dimethoxyethane (7.3 ml) was refluxed for 3 days. The solvent was evaporated in vacuo. To the residue was added 80% hydrazine monohydrate (1.2 ml) and then the mixture was refluxed with stirring for 0.8 hour. Water was added to the reaction mixture and then the resulting solid was collected by filtration. The solid was chromatographed on silica gel (20 ml) using a mixture of chloroform and methanol (40:1). The desired fractions were collected and evaporated in vacuo. The residue was recrystallized from ethyl acetate to give 3,5-diphenyl-1-(4-methoxybenzyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)pyrazole (0.15 g).

mp : 200-203°C

IR (Nujol) : 1645, 1580, 1505 cm^{-1}

NMR (DMSO-d_6, δ) : 3.70(3H, s), 5.24(2H, s),
6.71(1H, d, J=9.8Hz), 6.82-6.87(2H, m), 6.98-7.04(3H, m),
7.30-7.50(10H, m), 12.98(1H, s)

Analysis Calcd. for $C_{27}H_{22}N_4O_2 \cdot 1.1$-AcOEt :
C 70.97, H 5.84, N 10.54
Found : C 70.72, H 5.72, N 10.63

(+)-APCI/MS : 435 $(M + H)^+$

Example 31

A solution of 1-(4-methoxybenzyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenyl-3-[3-(2-phenylethoxy)phenyl]pyrazole (0.34 g), anisole (0.5 ml) and trifluoroacetic acid (1.1 ml) in 1,2-dichloroethane (2.2 ml) was refluxed with stirring for 10 hours. The mixture was

evaporated in vacuo. The residue was chromatographed on silica gel (20 ml) using a mixture of chloroform and ethyl acetate (3:1). The desired fractions were collected and evaporated in vacuo. The residue was recrystallized from a mixture of ethyl acetate and n-hexane to give 4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenyl-3-[3-(2-phenylethoxy)phenyl]pyrazole (0.12 g) as colorless crystals.

mp : 190-194℃

IR (Nujol) : 1680, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 2.95-3.10(2H, m), 4.17(2H, d, J=6.9Hz), 6.79-7.44(16H, m), 13.11(1H, s), 13.56(1H, s)

Analysis Calcd. for $C_{27}H_{22}N_4O_2$:

C 74.64, H 5.10, N 12.89

Found : C 74.88, H 5.01, N 12.93

(+)-APCI/MS : 435 $(M + H)^+$

Example 32

4-(3-Oxo-2,3-dihydropyridazin-6-yl)-3-phenylpyrazole was obtained in a manner similar to that of Example 31.

mp : 249-250℃ (DMF : H_2O)

IR (Nujol) : 3180, 1650, 1585 cm^{-1}

NMR (DMSO-d_6, δ) : 6.84(1H, d, J=9.8Hz), 7.29-7.48(6H, m), 7.85, 8.16(total 1H, each s), 12.94(1H, s), 13.26, 13.38(total 1H, each s)

Analysis Calcd. for $C_{13}H_{10}N_4O$:

C 65.54, H 4.23, N 23.52

Found : C 65.40, H 4.19, N 23.63

(+)-APCI/MS : 239 $(M + H)^+$

Example 33

To a mixture of 3,5-diphenyl-1-ethyl-4-(3-oxo-2,3-dihydropyridazin-6-yl)pyrazole (0.40 g), potassium tert-butoxide (144 mg), 18-crown-6 (31 mg) and dry tetrahydrofuran (10 ml) was added iodomethane (0.073 ml) at room temperature. After the mixture was stirred at room temperature for 4 hours, water was added to the mixture. The resulting solid was collected and recrystallized from a mixture of ethanol and water (1:2) to give 0.31 g of crystals of 3,5-diphenyl-1-ethyl-4-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yl) pyrazole.

mp : 129-130℃

IR (Nujol) : 1645, 1580 cm^{-1}

NMR (DMSO-d_6, δ) : 1.33(3H, t, J=7.2Hz), 3.49(3H, s), 4.08(2H, q, J=7.2Hz), 6.76(1H, d, J=9.5Hz), 6.99(1H, d, J=9.5Hz), 7.33-7.53(10H, m)

Analysis Calcd. for $C_{22}H_{20}N_4O$:

C 74.14, H 5.66, N 15.72

Found : C 73.76, H 5.60, N 15.73

(+)-APCI/MS : 357 $(M + H)^+$

Example 34

3,5-Diphenyl-1-isobutyl-4-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yl)pyrazole was obtained in a manner similar to that of Example 33.

mp : 126-128℃ (AcOEt : n-hexane)

IR (Nujol) : 1655, 1585 cm^{-1}

NMR ($CDCl_3$, δ) : 0.84(6H, d, J=6.7Hz), 2.15-2.38(1H, m), 3.60(3H, s), 3.90(2H, d, J=7.4Hz), 6.65(1H, d, J=9.5Hz), 6.80(1H, d, J=9.5Hz), 7.32-7.57(10H, m)

Analysis Calcd. for $C_{24}H_{24}N_4O \cdot 1/4H_2O$:

C 74.11, H 6.35, N 14.40

Found : C 74.28, H 6.34, N 14.32

(+)-APCI/MS : 385 $(M + H)^+$

Example 35

3,5-Diphenyl-4-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yl)-1-n-pentylpyrazole was obtained in a manner similar to that of Example 33.

oil

IR (filum) : 1645, 1580 cm^{-1}

NMR ($CDCl_3$, δ) : 0.83(3H, t, J=6.5Hz), 1.18-1.29(4H, m), 1.79-1.87(2H, m), 3.60(2H, s), 4.10(2H, t, J=7.5Hz), 6.66(1H, d, J=9.5Hz), 6.81(1H, d, J=9.5Hz), 7.34-7.57(10H, m)

(+)-APCI/MS : 399 $(M + H)^+$

Example 36

To a mixture of 3,5-diphenyl-1-(4-methoxybenzyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)pyrazole (0.50 g), potassium tert-butoxide (140 mg), 18-crown-6 (30 mg) and dry tetrahydrofuran (10 ml) was added iodomethane (0.12 ml) at room temperature. After the mixture was stirred at room temperature for 24 hours, it was partitioned between ethyl acetate and water. The separated ethyl acetate layer was washed with water and brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated in vacuo to give 3,5-diphenyl-4-(2-isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-1-(4-methoxybenzyl)pyrazole (0.47 g) as an oil.

IR (film) : 1660, 1600, 1590 cm^{-1}

NMR ($CDCl_3$, δ) : 0.99(6H, d, J=6.6Hz), 3.77(3H, s),

5.13(1H, sep, J=6.6Hz), 5.21(2H, s), 6.63(1H, d, J= 9.5Hz),
6.76-6.82(3H, m), 7.03-7.08(2H, m), 7.20-7.55(10H, m)

(+)-APCI/MS : 477 $(M + H)^+$

Example 37

A mixture of 3,5-diphenyl-4-(2-isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-1-(4-methoxybenzyl)pyrazole (0.44 g), anisole (0.9 ml), trifluoroacetic acid (2.2 ml) and 1,2-dichloroethane was refluxed for 2 hours. After the solvent was evaporated in vacuo, the residue was purified by column chromatography on silica gel using a mixture of n-hexane and ethyl acetate (25:1) as an eluent to give 3,5-diphenyl-4-(2-isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)pyrazole (0.19 g) as crystals.

mp : 220-222℃ (AcOEt : n-hexane)

IR (Nujol) : 3150, 1640, 1575, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 1.08(6H, d, J=6.6Hz),
5.11(1H, seq, J=6.6Hz), 6.81(1H, d, J=9.5Hz),
7.04(1H, d, J=9.5Hz), 7.31-7.44(10H, m), 13.60(1H, s)

Analysis Calcd. for $C_{22}H_{20}N_4O \cdot 1/2H_2O$:
C 72.31, H 5.79, N 15.33
Found : C 72.33, H 5.67, N 15.15

(+)-APCI/MS : 357 $(M + H)^+$

Example 38

A mixture of 3-(3-methoxyphenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenylpyrazole (0.22 g), 30% hydrogen bromide in acetic acid (2 ml), and 4.8% hydrogen bromide in water (2 ml) was refluxed with stirring for 16 hours. The reaction mixture was diluted with water and made basic with 28% ammonia in water. The resulting solid was

collected by filtration, which was recrystallized from a mixture of ethanol and water to give 3-(3-hydroxyphenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenylpyrazole (0.14 g).

mp : >250°C (EtOH : H_2O)

IR (Nujol) : 3275, 1650, 1580, 1550, 1525 cm^{-1}

NMR (DMSO-d_6, δ) : 6.65-6.90(4H, m), 7.11-7.43(7H, m), 9.44, 9.64(total 1H, each s), 13.06(1H, s), 13.50(1H, s)

Analysis Calcd. for $C_{19}H_{14}N_4O_2 \cdot 1/2H_2O$:

C 67.25, H 4.46, N 16.51

Found : C 67.53, H 4.11, N 16.59

(+)-APCI/MS : 331 $(M + H)^+$

Example 39

3-(3-tert-Butyldimethylsilyloxyphenyl)-4-(3-oxo-2,3-dihydropyridazin-6-yl)-5-phenylpyrazole was obtained in a manner similar to that of Preparation 77.

mp : 167-172°C (AcOEt : n-hexane)

IR (Nujol) : 3170, 1680, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 0.16(6H, s), 0.95(9H, s), 6.84-6.89(3H, m), 7.16-7.23(2H, m), 7.22-7.40(6H, m), 13.13(1H, s), 13.71(1H, s)

(+)-APCI/MS : 445 $(M + H)^+$

Example 40

1-(4-Methoxybenzyl)-5-(3-oxo-2,3-dihydropyridazin-6-yl)-3-phenylpyrazole was obtained in a manner similar to that of Example 1.

mp : 161-163°C ($CHCl_3$: n-hexane)

IR (Nujol) : 1650, 1595, 1520, 1505 cm^{-1}

NMR (DMSO-d_6, δ) : 3.69(3H, s), 5.65(2H, s), 6.85(2H, m),

6.95-7.19(3H, m), 7.32-7.48(5H, m), 7.82-7.98(2H, m),
13.30(1H, s)

Analysis Calcd. for $C_{21}H_{18}N_4O_2 \cdot 0.6CHCl_3$:
C 60.33, H 4.36, N 13.03
Found : C 60.04, H 4.31, N 12.91

(+)-APCI/MS : 359 $(M + H)^+$

Example 41

3,4-Diphenyl-1-(4-methoxybenzyl)-5-(3-oxo-2,3-dihydropyridazin-6-yl)pyrazole was obtained in a manner similar to that of Example 1.

mp : 221-223℃ (AcOEt : n-hexane)

IR (Nujol) : 1650, 1590, 1505 cm^{-1}

NMR (DMSO-d_6, δ) : 3.71(3H, s), 5.40(2H, s),
6.74(1H, d, J=9.8Hz), 6.85-6.92(3H, m), 7.10-7.39(12H, m),
13.39(1H, s)

Analysis Calcd. for $C_{27}H_{22}N_4O_2$:
C 74.64, H 5.10, N 12.89
Found : C 74.36, H 5.28, N 12.85

(+)-APCI/MS : 435 $(M + H)^+$

Example 42

5-(3-Oxo-2,3-dihydropyridazin-6-yl)-3-phenylpyrazole was obtained in a manner similar to that of Example 31.

mp : 206-208℃ (DMF : H_2O)

NMR (DMSO-d_6, δ) : 7.00(1H, d, J=9.8Hz), 7.12(1H, s),
7.33-7.51(3H, m), 7.84(2H, d, J=7.0Hz),
8.00(1H, d, J=9.8Hz), 13.48(1H, s), 13.58(1H, s)

Analysis Calcd. for $C_{13}H_{10}N_4O \cdot H_2O$:
C 60.93, H 4.72, N 21.86

Found : C 60.79, H 4.70, N 21.85

(+)-APCI/MS : 239 $(M + H)^+$

Example 43

3,4-Diphenyl-5-(3-oxo-2,3-dihydropyridazin-6-yl)pyrazole was obtained in a manner similar to that of Example 31.

mp : >250℃ ($CHCl_3$: MeOH)

IR (Nujol) : 3240, 1670, 1650, 1590, 1550, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 6.87(1H, d, J=9.9Hz), 7.16-7.30(11H, m), 13.00(1H, broad s), 13.59(1H, broad s)

Analysis Calcd. for $C_{19}H_{14}N_4O \cdot 1/4H_2O$:

C 71.57, H 4.58, N 17.57

Found : C 71.28, H 4.39, N 17.59

Example 44

5-Methyl-4-(3-oxo-2,3,4,5-tetrahydropyridazin-6-yl)-3-phenylpyrazole was obtained in a manner similar to that of Example 5.

mp : 223-225℃ (AcOEt)

IR (Nujol) : 3170, 1660, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 2.29(3H, s), 2.33-2.45(4H, m), 7.39-7.52(5H, m), 10.75(1H, s), 12.91(1H, s)

Analysis Calcd. for $C_{14}H_{14}N_4O \cdot 1/10AcOEt$:

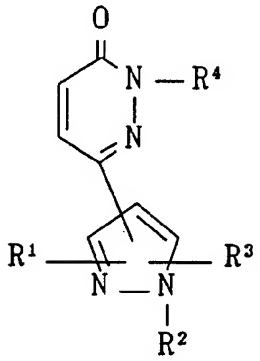
C 65.74, H 5.67, N 21.36

Found : C 65.78, H 5.71, N 21.06

(+)-APCI/MS : 255 $(M + H)^+$

CLAIMS

1. A pyrazole compound of the formula (I):



(I)

wherein R^1 and R^3 are the same or different and each is independently hydrogen, lower alkyl, ar(lower)alkyl, heterocyclic group, or aryl which may have one or more suitable substituent(s),

R^2 is hydrogen, lower alkyl, or ar(lower)alkyl which may have one or more suitable substituent(s), and

R^4 is hydrogen or lower alkyl,

or a salt thereof.

2. The compound of claim 1, wherein

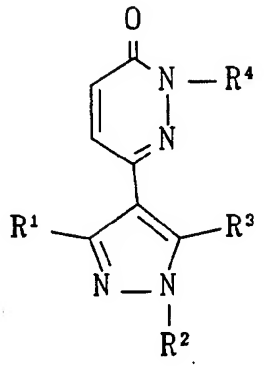
R^1 and R^3 are the same or different and each is independently hydrogen; lower alkyl; phenyl(lower)alkyl; unsaturated 3 to 8-membered heteromonocyclic group containing an oxygen atom; or phenyl which may have 1 to 3 suitable substituent(s) selected from the group consisting of halogen, lower alkyl, lower alkoxy, hydroxy, lower alkyl-silyloxy, phenyl(lower)alkoxy, and phenyl which may have halo(lower)alkyl;

R^2 is hydrogen, lower alkyl, or phenyl(lower)alkyl which may have lower alkoxy, and

R^4 is hydrogen or lower alkyl,

or a salt thereof.

3. The compound of claim 2, which is shown by the formula (I'):



(I')

wherein R^1, R^2, R^3 and R^4 are each as defined in claim 2,
or a salt thereof.

4. The compound of claim 3, wherein

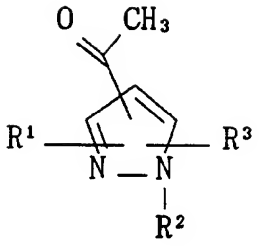
R^1 and R^3 are the same or different and each is independently phenyl which may have 1 to 3 suitable substituent(s) selected from the group consisting of halogen, lower alkyl and lower alkoxy, and

R^2 and R^4 are the same or different and each is independently hydrogen or lower alkyl,
or a salt thereof.

5. The compound of claim 4, wherein R^1 and R^3 are each as defined in claim 4, and R^2 and R^4 are each hydrogen, or a salt thereof.

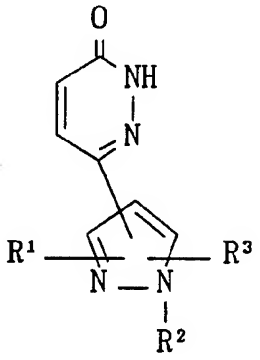
6. A process for the preparation of the pyrazole compound of claim 1 or a salt thereof, which comprises,

(1) subjecting a compound of the formula (II):



(II)

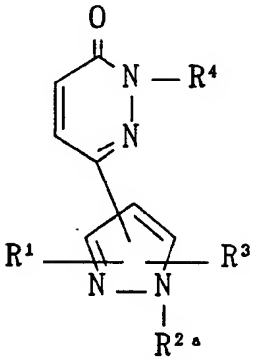
wherein R^1, R^2 and R^3 are each as defined in claim 1, or a salt thereof, to formation reaction of pyridazinone ring, to give a compound of the formula (Ia):



(Ia)

wherein R^1, R^2 and R^3 are each as defined in claim 1, or a salt thereof,

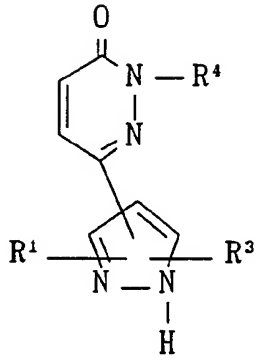
(2) subjecting a compound of the formula (Ib):



(Ib)

wherein R^1, R^3 and R^4 are each as defined in claim 1, and R^{2a} is ar(lower)alkyl, or a salt thereof, to elimination reaction of

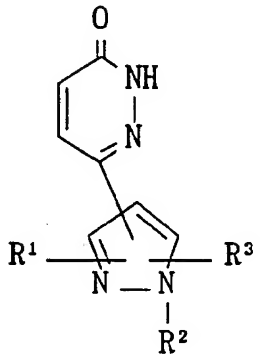
ar(lower)alkyl group, to give a compound of the formula (Ic):



(Ic)

wherein R^1, R^3 and R^4 are each as defined in claim 1, or a salt thereof, or

(3) reacting a compound of the formula (Ia):



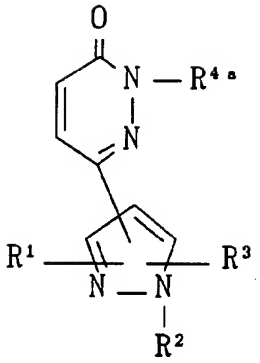
(Ia)

wherein R^1, R^2 and R^3 are each as defined in claim 1, or a salt thereof, with a compound of the formula :

$$R^{4a} - X$$

wherein R^{4a} is lower alkyl, and X is a leaving group,

to give a compound of the formula (Id):



(Id)

wherein R^1, R^2 and R^3 are each as defined in claim 1, and R^{4a} is as defined above, or a salt thereof.

7. A pharmaceutical composition comprising the compound of claim 1 or a salt thereof in association with pharmaceutically acceptable carriers or excipients.

8. A method for preventing or treating a disease selected from the group consisting of ischemic heart diseases, peripheral vascular diseases, cerebral ischemia, migraine, diabetes, depression, and Parkinson's disease, which comprises administering the compound of claim 1 or a salt thereof to a human being or an animal.

9. Use of the compound of claim 1 or a salt thereof as a medicament.

10. Use of the compound of claim 1 or a salt thereof as an adenosine antagonist.

11. A process for preparing a pharmaceutical composition which comprises admixing the compound of claim 1 or a salt thereof with pharmaceutically acceptable carriers or excipients.

INTERNATIONAL SEARCH REPORT

Internatior Application No
PCT/JP 96/01747

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D403/04 A61K31/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 220 735 (RICHTER GEDEON) 6 May 1987 see page 26; claims; table 7 ---	1-7
A	EP,A,0 175 363 (CASSELLA) 26 March 1986 see page 27 - page 30; claims -----	1-7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 August 1996	04.09.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatio Application No
PCT/JP 96/01747

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-220735	06-05-87	AU-B-	589698	19-10-89
		AU-B-	6449686	07-05-87
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		DE-A-	3688450	24-06-93
		ES-T-	2058054	01-11-94
		JP-B-	1001475	11-01-89
		JP-C-	1522192	12-10-89
		JP-A-	62161768	17-07-87
		US-A-	4826845	02-05-89
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		DE-A-	3522193	02-01-87
		AU-B-	4766185	10-04-86
		JP-A-	61085367	30-04-86
		US-A-	4816454	28-03-89